Quality by Design

A discussion on applicability in Pharmaceutical Testing

Sudhir Goudar
Head Compliance and Auditing
Novartis Pharmaceuticals,
Singapore

18 Oct 2013

Quality by Design (QbD)

- QbD, as defined in ICH Q8(R2), “it is a systematic approach to pharmaceutical development beginning with predefined objectives that emphasize product and process understanding as well as product and process control”
- Quality by Design (QbD) is emerging to enhance the assurance of safe, effective drug supply to the consumer, and also offers promise to significantly improve manufacturing quality performance

The beginning...

- Quality could be planned and most of the problems relate to the way, in which Quality is planned in the first place – Juran
  - Primarily started with automotive industry
  - Pharma industry / regulators adopted to see how drugs are discovered, developed and manufactured commercially
- Ultimate goal of QbD
  - Embed quality into Pharmaceutical products to protect patient safety
  - Predefined product quality, safety and efficacy by design

Why now?

- To enhance quality of knowledge to ensure methods are robust and rugged
  - Target is specified and is achievable through monitoring of process parameters
  - Allows flexibility to modify within a set of tested parameters
  - Provides structured approach to drug development and tech transfer
  - Failures understood with specific root cause analysis
  - Reduced cost/ rework and Delivery speed to the market
  - Regulatory!

FDA and EMA announcement

"Description of the manufacturing process in regulatory submissions must be the same whether the applicants use Quality by Design or the traditional approach"

- Pilot program launched in March 2011 to assess QbD approach that uses statistical, analytical and risk-assessment methods to ensure quality in manufactured drugs.
- First conclusions in August 2013- both the agencies require details in the manufacturing process description
- Critical steps in manufacturing process should be described (identified, controlled or monitored) to ensure quality
- List of CQAs for drug substance, and excipients with a discussion in relation to finished product to be described

On the way...

"Quality Metric Requirement"
coming soon for Drug Manufacturers

- The FDA plans to require drug manufacturers to submit quality metrics data to improve post-market surveillance on quality
  - Batch failure rates or complaint data
  - Use the data to target its inspections
- One possible upside for manufacturers: better performing companies could face fewer inspections and faster regulatory approvals for certain applications.

Current approach QbD approach

- Quality is assured by testing and inspection.
- Data intensive submission which includes disjointed information without “big picture”.
- Specifications are based on batch history.
- “Frozen process,” - discourage changes.
- Focuses on reproducibility which often avoids or ignores variation.

- Quality is built into product & process by design based on scientific understanding.
- Knowledge rich submission which shows product knowledge & process understanding.
- Specifications based on product performance requirements.
- Flexible process within design space which allows continuous improvement.
- Focuses on robustness which understands and control variation.

Applying QbD to Pharmaceuticals

- Early Development phase I & II a
  - Product performance/ Batch to batch reproducibility
- Late Development Phase II b/III
  - Robust method capability of being sensitive to CQA
- Post Commercial Filing/ Phase IV
  - Site transfers, product enhancement, continuous improvement

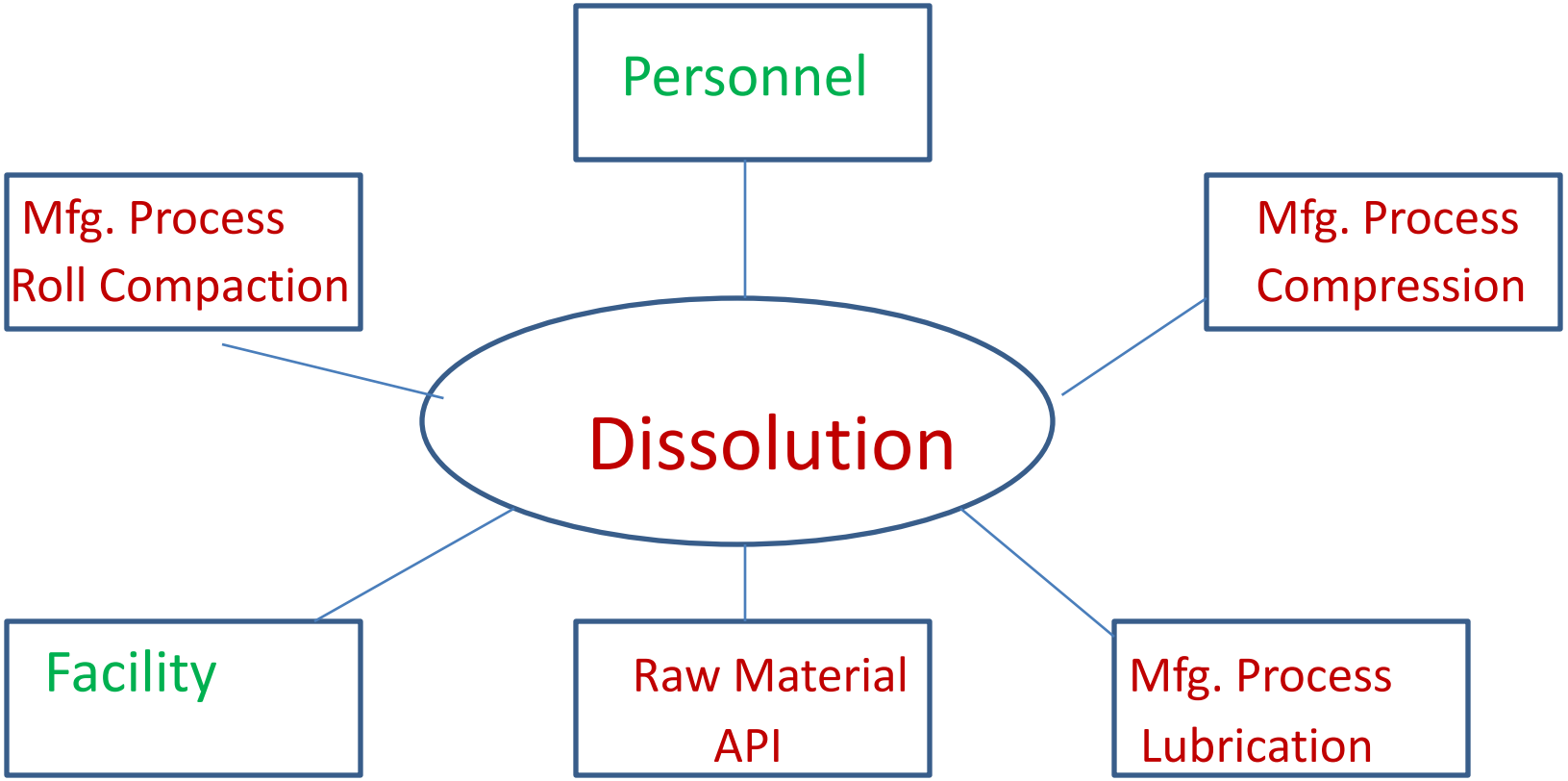
Applying QbD to Analysis

- Flexible regulatory approach where possible
  - QbD approach is an effort to introduce post-approval changes without prior regulatory approval and
  - End-product batch testing can be replaced/reduced by real time release based on understanding of design
- Dissolution becomes a key tool for understanding product performance and for measuring the impact of changes in input parameters or process.

Dissolution testing

- Dissolution is a common performance test employed by the Pharma industry to design/ develop and release products and used as a measure of formulation bio performance
- It is considered as an important test method to monitor impact of environmental storage conditions and manufacturing process on the rate of drug release from the dosage form.

Walking through the manufacturing process....



CQA

- Critical quality attribute (CQA)
  - A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality
- Analytical Target Profile (ATP).
  - The incorporation of this concept in the development cycle reduces the burden of post approval variations

Identify CQAs

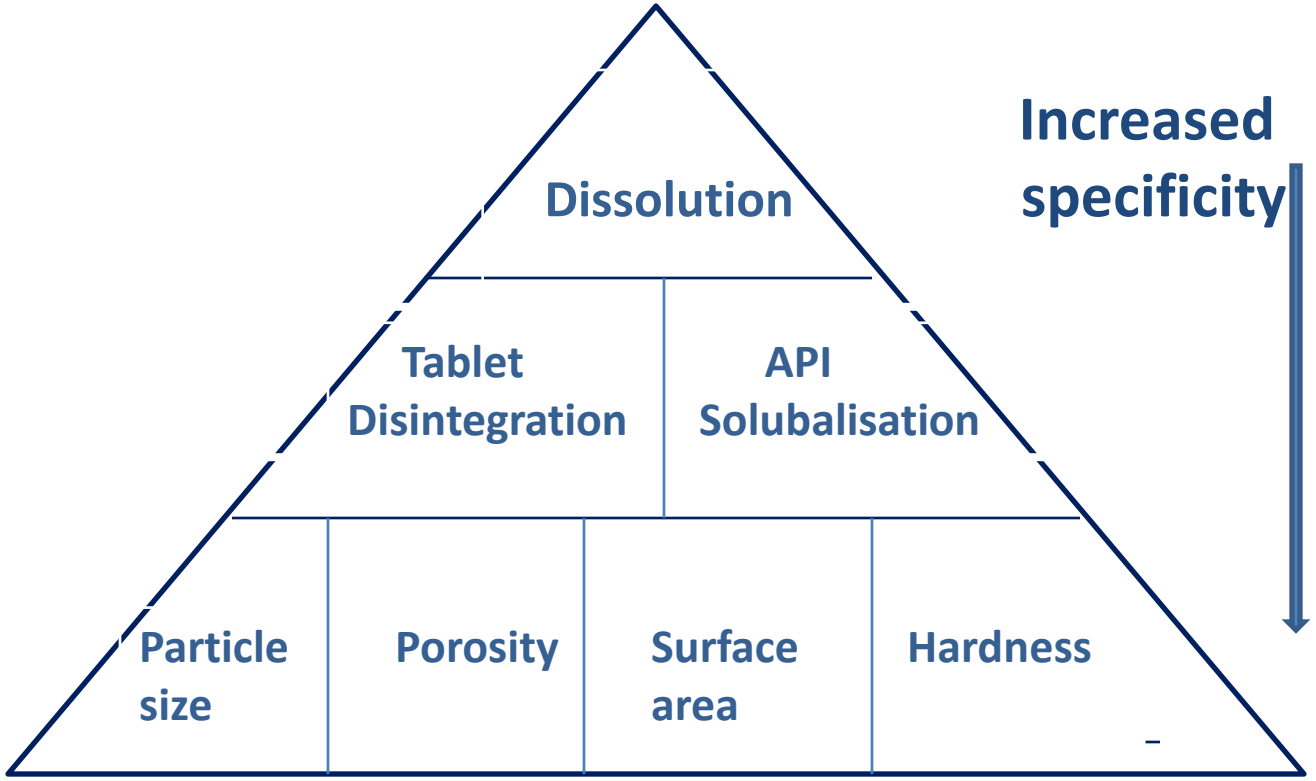
Quality attributes	Target	CQA	Justification
Appearance, Odor	No visual defects No unpleasant odor	No No	Not directly linked to safety or efficacy of the product
Friability	Not more than 1.0% w/w	No	Compendia requirement but not lined to product safety or efficacy
Assay	100% of label claim	Yes	Variability in assay will affect safety and efficacy; therefore, assay is critical
Content uniformity	Meets compendia requirements	Yes	Variability in content uniformity will affect safety and efficacy.
Degradation products	Meets compendia requirements	Yes	Critical to drug safety

Dissolution testing

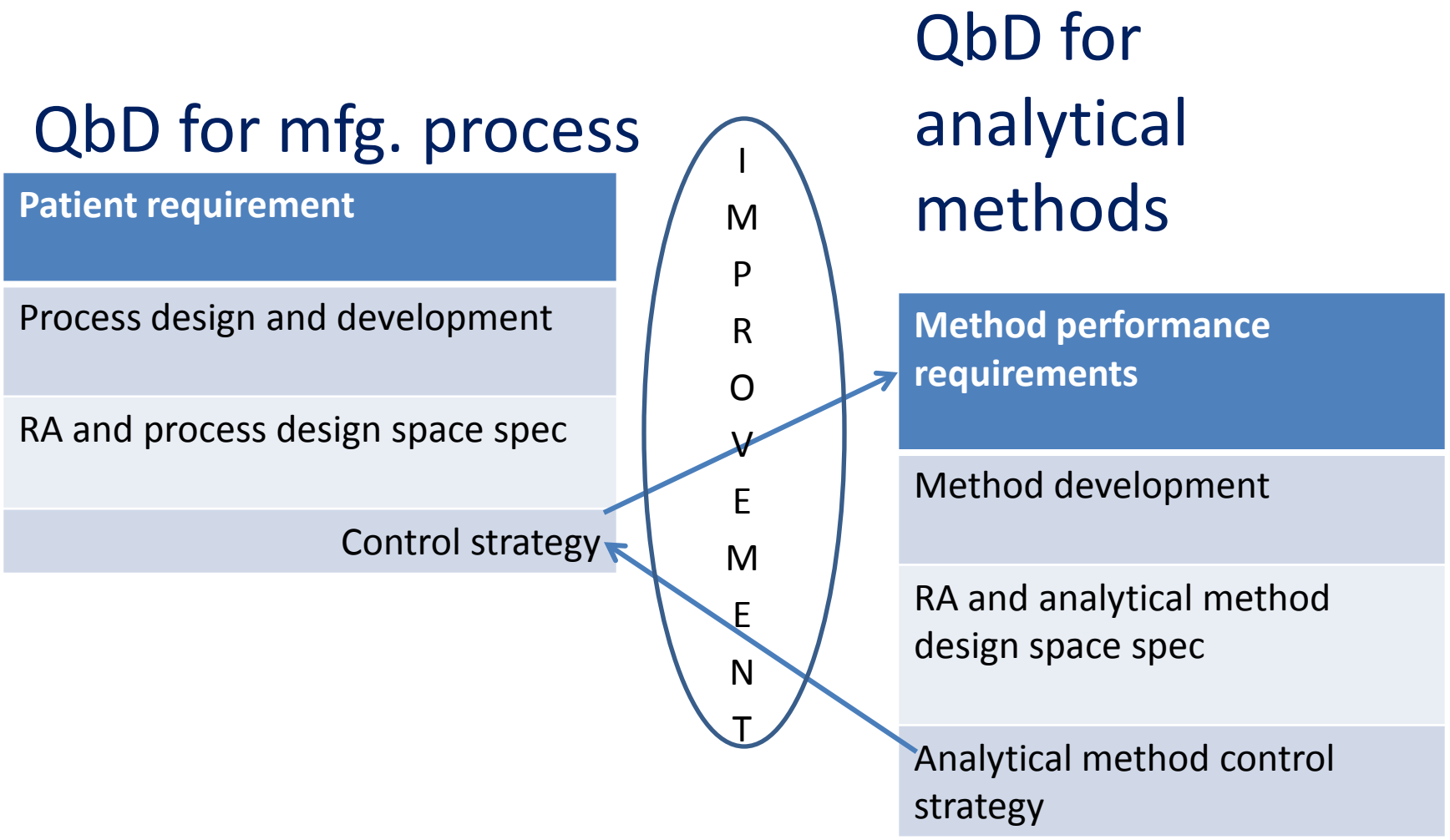
QbD can be applied to

- Dissolution test parameters
  - Dissolution Conditions – Selection of Key Operational Parameters
- The end detection
  - Detection Technique – Develop Analytical Design Space
- The product development/ control strategy .
  - Science Based Application - Understand performance mechanism, apply as control Strategy, as CQA

Dissolution testing



Mfg v/s Analytical method



Approach for analytical method development

- Method design
  - Performance requirements
- Method development
  - DoE
  - Qualify
- Define controls
  - Risk assessment and define method space
- Verify controls/ life cycle knowledge management/ continuous improvement

Method Design

- Establishing the method performance requirements
  - Prior experience, geographic limitations and/or availability of reagents, specific technologies in laboratories
  - Factors that can influence the performance of an analytical method can be mapped against the unit operations within the method

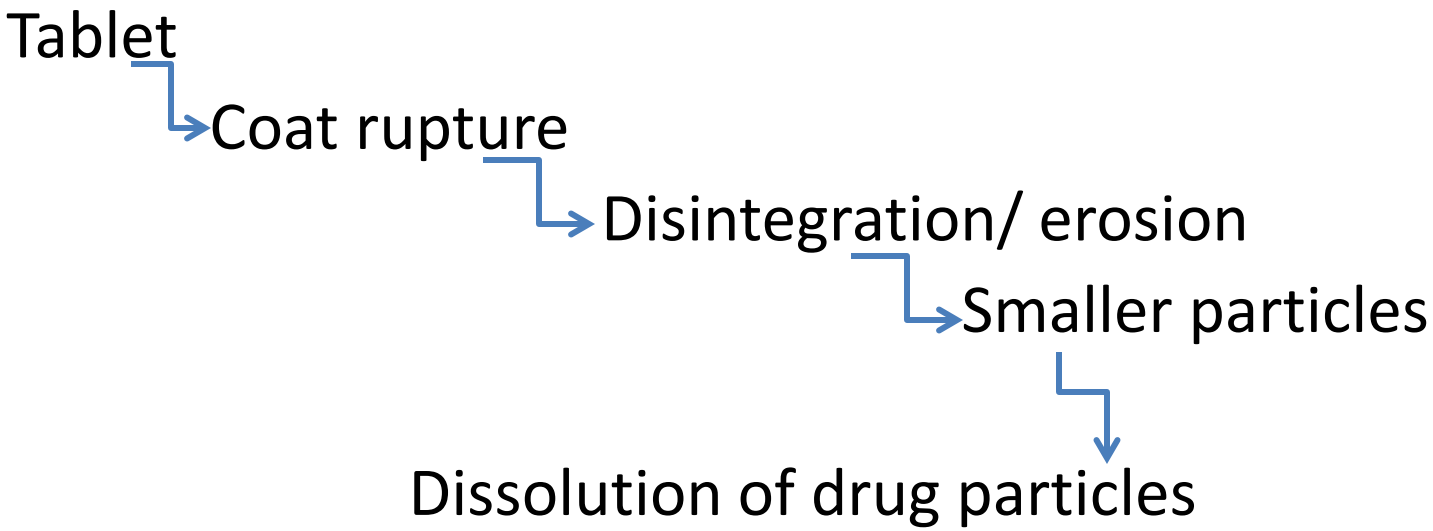
Define target requirements

- Define target requirements
  - For example for a simple IR formulation: > 75% dissolved at 30 minutes
  - Analytical measurement must be (designing spec)
  - Linear (R2 > 0.999 conf. interval of +/-0.5% around intercept)
  - Must be accurate (> 98%)
  - Must Repeatable (< 5% RSD)
  - Must be Reproducible...

Method development

- What are the rate-limiting and quality critical attributes?

Breaking Down the Dissolution Process:



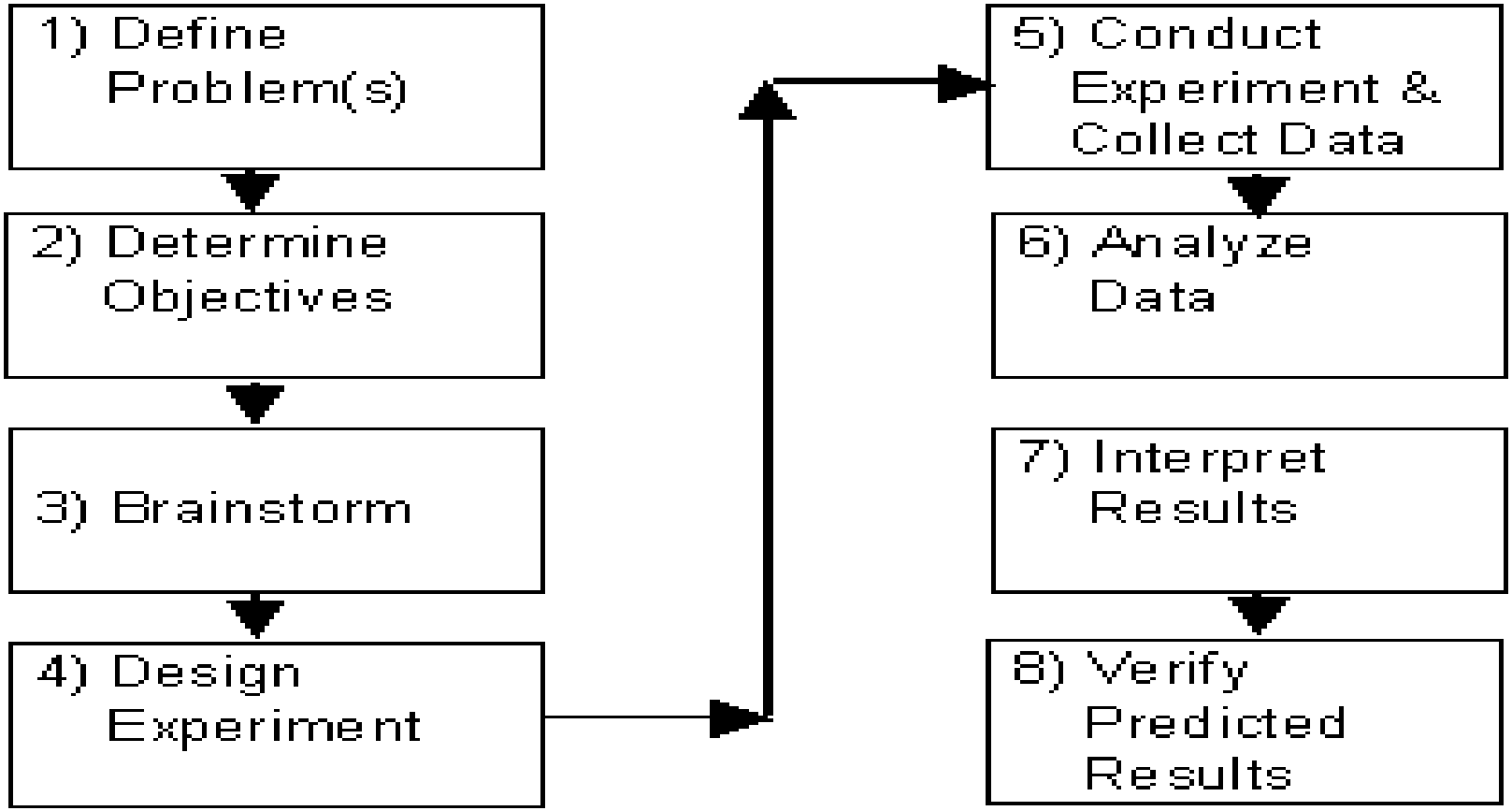
Method development

- Is there an existing method? Review
- Some of the possible selections:
  - Apparatus
  - Dissolution medium
  - Stirring speed
  - Analytical technique (HPLC / UV)
  - Solubility (pH, surfactant needed?)

DoE or Experimental Design

- The experimental design is defined as the systematic procedure carried out under controlled conditions in order to discover an unknown effect, to test or establish a hypothesis, or to illustrate a known effect
- When analyzing a process, experiments are often used to evaluate **which process inputs have a significant impact** on the process output, and **what the target level of those inputs should be** to achieve a desired result (output)
- Experiments can be **designed** in many different ways to collect this information.

DoE process map



Advantages

- Reduce product material and labor complexity
- Reduce late engineering design changes
- Reduce design costs by speeding up the design process
- Reduce rework, scrap, and the need for inspection

Method development

- Method qualification
  - Factors that have been identified as having a potential impact on method performance are evaluated
  - A preliminary assessment of the potential impact of the factors may also be explored using a robustness screening design

Define controls

- List all method parameters in a group brainstorming session
  - Equipment
  - Environment
  - Method
  - Measurement
  - Materials
  - Combine this with a “walkthrough”of the method

Optimising the design...

- Identify potential variables
- Reduce variability
- Optimise critical variables

- Materials
- Dissolution bath
- Buffer media
- Measures
- Sampling
- Laboratory
- Product
- ……..

Define controls

Carry out Risk Assessment

- Rank the experimental factors in terms of risk
  - Frequency
  - Probability of detection
- Impact on method performance
  - Accuracy
  - Linearity
  - Precision
- Prioritize in the order of risk

Define controls

- Method control strategy
  - Define final operating parameters
  - Define parameters range to ensure performance of the analytical method
  - Implement changes via change control process to ensure control of the established method parameters.

Control strategy shall ensure...

- A consistent performance of the method throughout its life cycle
- Flexibility to perform a qualification against the specific ATP
- Result in more robust methods which produce consistent, reliable and quality data throughout the life cycle
- Less method incidents in routine environment
- Less time spent on investigations with RCA known

Verify Controls

Continuous improvement/life-cycle knowledge management:

- Establish repository to capture the information generated (e.g., factors considered, risk-assessment tools used to select variables for experimental study, and outcomes from each study
- Change control in place to assess impact of any proposed future changes to the analytical method
- Include RA to identify any risk to changes performed
- Additionally, as appropriate, method equivalency experiments may be included to further justify the proposed changes

Other factors

- Handling and storage of samples
- Accuracy/ calibration of instruments used in the testing
- Register method performance criteria as opposed to specific method conditions
- Well written procedures
- Training of personnel
- Promote continuous improvement

Summary

- A dynamic QbD program
  - Capitalises on process monitoring
  - Employs appropriate mathematical models
  - Establish parametric based specification
  - Defines clinically relevant design space
  - Facilitate real time release testing
  - Eliminates QC waste
  - Provides mechanism to update control strategies and
  - Above all recoginse the multivariate nature of quality

Thank you

- Back up slides

Risk analysis by FMEA

Relative Rank[4]	Factor	Variables	Potential Effect	Ruggedness Experiment Design Element
1	UV flow cells	Pathlength	Inaccurate results Variable results Failed transfer	Vary instruments at each of three sites and allow flowcell to vary
2	Standard Preparation	Technique	Inaccurate results Failed system suitability	Investigated alternate standard preparation – see Section 2
3	MultiDose apparatus	Tablets not dropping/sticking to wall Cleanliness of media tank Tubing dead volume Lids/no lids on sample carousel	Inaccurate results OOS/Questionable results Re-runs due to failing to meet USP sampling windows	Vary instruments at each of three sites and allow to vary
4	Tween	Manufacturer, grade, age, lot	Inaccurate results	Vary Tween at each of three sites and allow to vary
5	Environment	Tablet condition after sitting in carousel awaiting analysis	Inaccurate results OOS/Questionable results	Allow to vary

Define controls

Parameter	Impact on Method Performance	Rationale for Impact Assessment	Classification	Design Space	Suggested Action
HCl Concentration	Yes	Affects % dissolved and discrimination between batches	B	± 10% from nominal	Ensure HCl concentration is in range.
Tween Concentration	Yes	Affects % dissolved and discrimination between batches	B	± 5% from nominal	Ensure Tween concentration is in range.
Flowcell Pathlength	Yes	Variation in pathlength can result in inaccurate results. Use of 5 different apparatus in ruggedness exercise produced negligible variation in results.	B	± 2% from nominal	Ensure that flowcell pathlength is within range.
Standard Preparation Technique	Yes	Inadequate standard dissolution can produce inaccurate results.	D	Operator must ensure that all standard is dissolved before proceeding.	Method revised to include a different validated standard preparation technique.

Define controls

Standard Weighing Technique	Yes	Standard solution degrades upon extended contact with aluminium weigh boat.	D	Operator must not immerse or store aluminium weight boat in standard solution.	Method revised to exclude extended storage of standard solutions containing aluminium weigh boats.
Multidose Apparatus	No	Use of 5 different apparatus in ruggedness exercise produced negligible variation in results.	C	Any	None
Tween Manufacturer, Grade, Lot	No	Sample preparation by 5 different operators at 3 sites in ruggedness exercise produced negligible variation in results.	E	Any	None
Environment	No	Use of 5 different apparatus at 3 sites in ruggedness exercise produced negligible variation in results.	C	Any	None
Operator	No	Use of 6 different operators in ruggedness exercise produced negligible variation in results.	C	Any	None[2]

Check where to insert this

- **1.3 Quality Target Product Profile for the ANDA Product**
- *Note to Reader: The quality target product profile (QTPP) is "a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product." 1 The QTPP is an essential element of a QbD approach and forms the basis of design of the generic product. For ANDAs, the target should be defined early in development based on the properties of the drug substance (DS), characterization of the RLD product and consideration of the RLD label and intended patient population. The QTPP includes all product attributes that are needed to ensure equivalent safety and efficacy to the RLD. This example is for a simple IR tablet; other products would include additional attributes in the QTPP. By beginning with the end in mind, the result of development is a robust formulation and manufacturing process with a control strategy that ensures the performance of the drug product.*

1.4 Dissolution Method Development and Pilo

Note to Reader: A pharmaceutical development report should do dissolution method used in pharmaceutical development. This me from the FDA-recommended dissolution method and the quality testing.

1.4.1 Dissolution Method Development

Acetriptan is a BCS Class II compound displaying poor aqueous mg/mL) across the physiological pH range. As such, developmen can act as the best available predictor of equivalent pharmacokin allow assessment of acetriptan tablets manufactured during devel