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QUALITY BY DESIGN AND PROCESS ANALYTICAL TECHNOLOGY: A CONCEPTUAL REVIEW OF CURRENT APPROACH AND ITS LIMITATIONS

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Abstract:

Quality by Design (QbD) brings quality to the fore from the very beginning of the product development and manufacturing process, improving efficiency as a result. After all, testing products at the end of the manufacturing process limits your options for correction. Quality cannot be tested into a product; it needs to be infused into it, by design. Combined with Process Analytical Technology (PAT), QbD enables forward-looking companies to move away from traditional quality approaches and instead employ systematic, data-driven strategies to deliver quality outcomes. [1,2]. In this review, our analysis reveals the following tools as the frequently adopted for conducting each activity: Quality Target Product Profile (QTPP), Critical Material Attributes (CMA), Critical Quality Attributes (CQA), Critical Process Parameter (CPP), Reference Listed Drug (RLD), Design Space, Design of Experiments (DoE), Risk Assessment (RA) and Mitigation/Minimization. Quality by Design, Formulation by Design, Analytical QbD. FDA initiative on process analytical technology. PAT as driver for improving quality and reducing costs: QbD, QA, QC and GAMP, PAT Guidance, Standards and Regulatory Requirements. The present paper deals on these two terms QbD and PAT.

Keywords: *Quality by Design; Risk Assessment; Design of Experiments; PAT; Design Space; ICH Q8*

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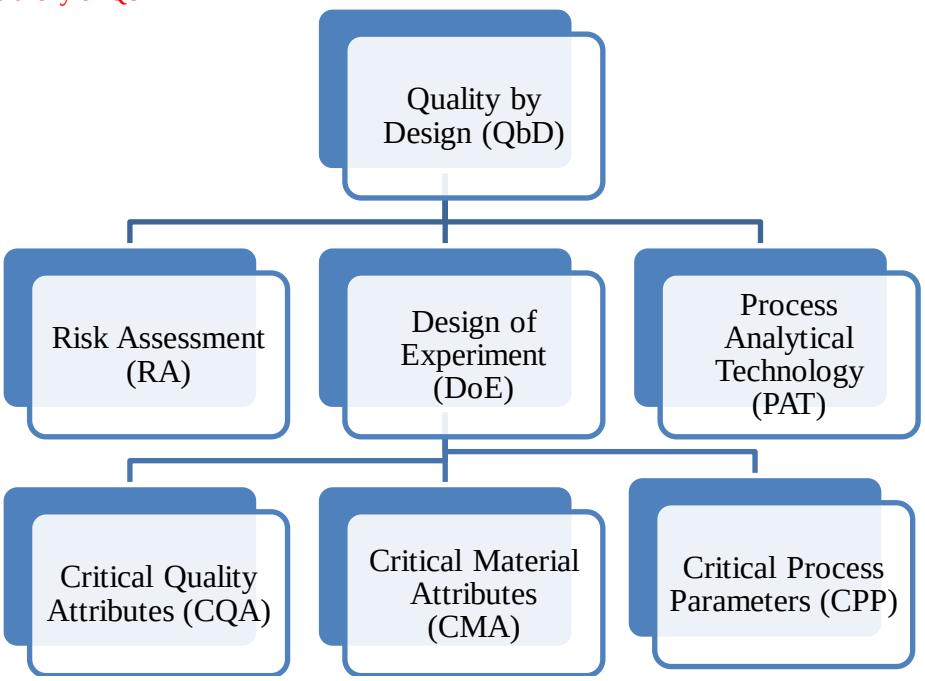
INTRODUCTION:

With the increasing competition at the global scale and the growing impact of information technology, pharmaceutical industry faces nowadays an urgent need to improve its operational performance and the overall quality of its products [1, 3, and 4]. Time to market, product quality, regulatory compliance, waste, cost reduction and cycle time are major concerns that must be addressed in a systematic manner [5, 6]. The Pharmaceutical sector is therefore undergoing an accelerated structural change driven not only by these needs but also pushed by the willingness of the regulatory authorities to accept novel approaches that can secure higher quality and product safety standards [5, 6]. QbD is currently seen as a key enabler for achieving the desired performance quantum leap (Figure 1) [7, 8].

The guiding principle is that Quality should begin before manufacturing starts and capital allocations are made. In practice, this means that companies should start by establishing their quality goals, develop products features that attain these goals, develop processes capable to deliver such products and establish controls that enable operations to be conducted consistently [9]. Therefore, QbD is focused on achieving customer requirements consistently and efficiently [9, 10]. This is a different perspective from Quality Improvement, for instance, focused on solving chronic problems and reducing normal causes of variability inherent to the process, after manufacturing starts [9, 10].

Figure 1: Hierarchy of QbD



The companies show less interest in identifying the root cause of manufacturing failures. Furthermore, no rationale-based approach is followed to predict the effects of scale-up on the final product [9, 10]. But with changing time and increasing complexity of regulatory requirements in the approval of a drug to come in market, companies are focusing on methods through which they can prepare a design of the product and do researches related to complexities that may have to be faced in future and thus find out the solutions prior to manufacturing. This study is done through various tools like QbD, PAT etc. The main reason behind is only one and that is to reduce the cost of manufacturing defects (Table 1 & 2).

Table 1: Differences between current approach and QbD approach [11].

Current Approach	QbD Approach
Quality is assured by testing and inspection.	Quality is built into product & process by design and based on scientific understanding
It includes only data intensive submission which includes disjointed information without "big picture"	It includes Knowledge rich submission which shows product knowledge & process understanding.
Here, any specifications are based on batch history	Here, any specifications based on product performance requirements.
Here there is "Frozen process," which always discourages changes.	Here there is Flexible process within design space which allows continuous improvement.
It focuses on reproducibility which often avoids or ignores variation.	It focuses on robustness which understands and control variation

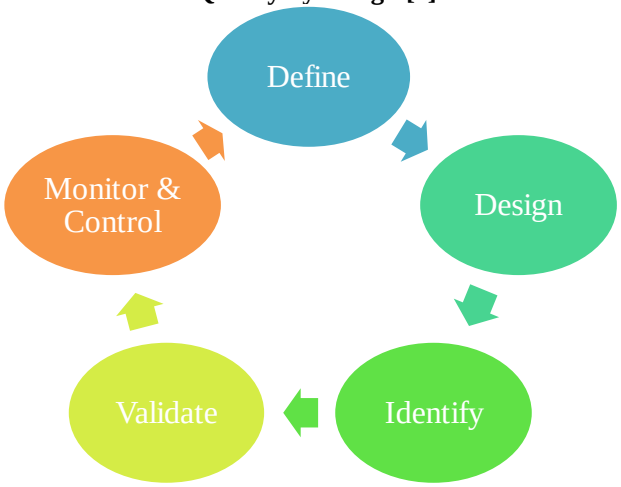
Table 2: Traditional approach & Enhanced QbD approach [12].

Aspects	Current	QbD
Pharmaceutical Development	Empirical, Random, Focus on optimization	Systematic, Multivariate experiments, Focus on control strategy and robustness
Manufacturing Process	Fixed	Adjustable within design space, managed by company's quality systems
Process Control	Some in-process testing	PAT utilized, Process operations tracked and trended
Product Specification	Primary means of quality control, based on batch data	Part of the overall quality control strategy, based on desired product performance
Control Strategy	By testing and inspection	Risk-based control strategy , real-time release possible

Quality by Design

It is defined as a systematic, holistic and proactive approach to pharmaceutical development, begins with pre defined objectives (Figure 2). It emphasizes product and process understanding and process control based on sound science and quality risk management [ICH Q8 (R2)].

Figure 2: Illustration of the different steps in development of a pharmaceutical product, Pharmaceutical Quality by Design [3].



QbD required for

a) Major amendments during review process
b) Exhibit batch stability failure, formulation revision
c) Longer time for generic product approval
d) Approved product may not be marketed
e) Post approval changes – prior approval supplements
f) Generic industry approach- File first learn later

Advantages of Adopting Quality by Design Approach [12]

- Cost efficient approach for delivering high quality drug substance and drug Product consistently.
- Product developed/built considering customer need.
- Robust process focuses on control strategy rather than testing.
- Overall development is systematic and multi variate experiments to understand the process and Product which establish 'Design space"
- Process is adjustable within the design space which is not the case with a fixed process.
- Product life cycle is managed as a preventive action rather than reactive problem solving
- Proper implementation of QbD can lead to savings in terms of time and money.
- Proper risk assessment is key to avoid more experimentation, testing and documentation.
- If control strategy and design space is well established then there will be definitely benefits considering the product scale up and commercialization which can eliminate the risk of product failure and consistency in the manufacturing.
- QbD approach can help to avoid delay in process validation.
- It ensure higher level of assurance of product quality for patient
- Improved product and process design & understanding
- Process can be changed within the design space which helps in avoiding updation of regulatory filings, variations and follow ups, time and money
- More efficient regulatory oversight, minimize/eliminate potential compliance actions
- QbD principles promote 'INNOVATION and CONTINUOUS IMPROVEMENT "of the Product

For industry

a) It helps in better understanding of the process.
b) It reduces batch failure.
c) It ensures better design of products with fewer problems in manufacturing.
d) It allows for continuous improvement in products & manufacturing process.
e) More efficient and effective control of change.
f) Return on investment / cost savings.

Additional opportunities: An enhance QbD approach to pharmaceutical development provides opportunities for more flexible regulatory approaches.

Ex: Manufacturing changes within the approved design space without further regulatory review.

a) Reduction of post-approval submissions.
b) Better innovation due to the ability to improve processes without resubmission to the FDA when remaining in the Design Space.
c) More efficient technology transfer to manufacturing.
d) Greater regulator confidence of robust products.
e) Risk-based approach and identification.
f) Innovative process validation approaches.
g) Less intense regulatory oversight and less post-approval submissions.
h) For the consumer, greater drug consistency.
i) More drug availability and less recall.
j) Improved yields, lower cost, less investigations, reduced testing, etc.
k) Time to market reductions: from 12 to 6 years realized by amongst others.
l) First time right: lean assets management.

For FDA

a) It enhances scientific base for analysis.
b) It provides better consistency.
c) It provides more flexibility in decision making.
d) It ensures decisions are made on scientific base & not on observed information.

A QbD development process may include (Figure 3)

- Define Quality Target Product Profile (QTPP)
- Define Critical Quality Attributes (CQAs)
- Perform Risk Assessment (RA)
- Link raw material attributes (CMAs) and
- Process parameters (CPPs) to CQAs
- Design and implement a control strategy

Figure 3: Elements of QbD

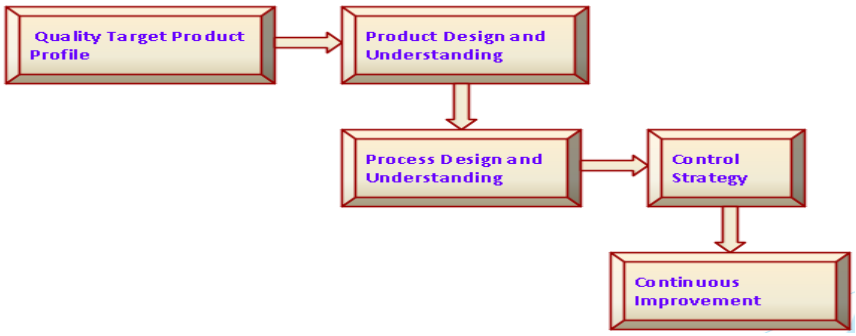
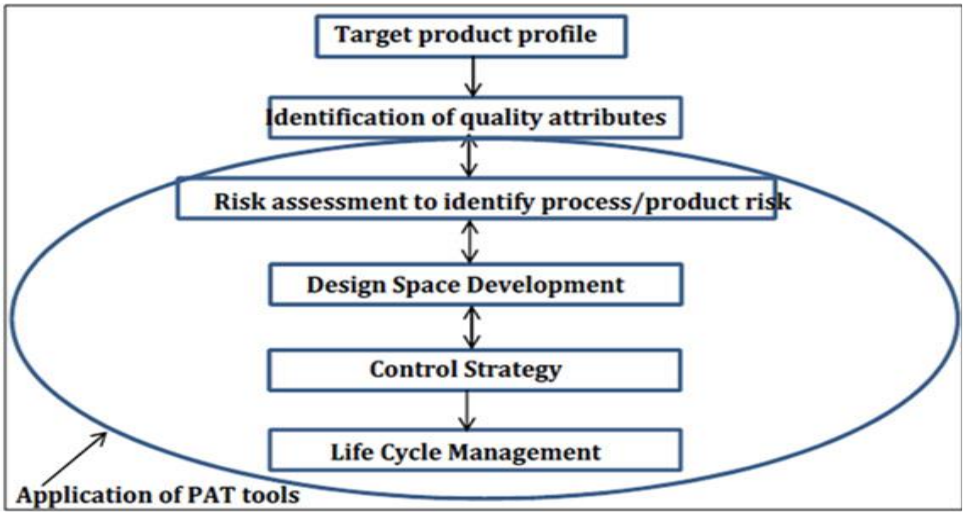


Figure 4: Manage product lifecycle, including continuous improvement [13]



a) It is started with a target product profile that illustrates the use, safety and efficacy of the product (Figure 4)
b) Then, introduces a target product quality profile that the formulators and process engineers use as a quantitative surrogate for aspects of clinical safety and efficacy of the product during development.
c) The collection of relevant prior knowledge about the drug substance, potential excipients and process operations into a knowledge space is also done.
d) Application of risk assessment tools to prioritize knowledge gaps for further investigation is necessary.
e) Formulation of a design to find the critical material (quality) attributes of the final product that is necessary to be controlled to meet the target product quality profile is then done.
f) Also formulate the design of manufacturing process to produce a final product having the required critical materials attributes.
g) Find out the critical process parameters and raw material attributes that should be controlled to achieve these critical material attributes of the final product.
h) Risk assessment must be used to prioritize process parameters and material attributes for experimental verification.
i) Combination of prior knowledge with experiments is important to establish a design space or other representation of process understanding.
j) Making of a control strategy for the entire process that must include raw material controls, process controls and monitors, design spaces around individual or multiple unit operations, and/or final product tests.

k) The control strategy must encompass expected changes in scale and can be guided by a risk assessment.
l) Monitoring and update of the process to assure consistent quality continually.

The Quality Target Product Profile (QTPP)

QTPP has been defined as a "prospective and dynamic summary of the quality characteristics of a drug product that ideally will be achieved to ensure that the desired quality, and thus the safety and efficacy, of a drug product is realized". It is a set of elements that defines the drug product, target or goal set in advance. It is a guide to Drug Product development. It covers dosage form and route of administration, dosage form strength (s), therapeutic moiety release or delivery and pharmacokinetic characteristics (e.g., dissolution and aerodynamic performance) appropriate to the drug product dosage form being developed and drug product quality criteria (e.g. sterility and purity) appropriate for the intended marketed product [14].

QTPP forms the basis for product design in the following way [15].

a) Dosage form
b) Route of administration
c) Strength, maximum and minimum
d) Release/delivery of the drug
e) Pharmacological characteristic
f) Drug product quality criteria
g) Pharmaceutical elegance

QTPP forms the basis for

- The Reference Listed Drugs (RLD) and its label
  - A Reference Listed Drug (RLD), as goes by its innate meaning, is an FDA approved drug product which can be referred to by a generic drug manufacturer while filing an Abbreviated New Drug Application (ANDA). An RLD is basically useful to establish bioequivalence of the product with that of an already approved one.
  - When a generical manufacturer is filing an ANDA, they should refer to the FDA designated RLD in the application portraying that the proposed generic drug is the same with respect to the active ingredient(s), dosage form, route of administration, strength, labelling, and conditions of use, along with other characteristics.
  - Generally, an innovative product or brand name product is designated as an RLD. But with the time, when generic products enter the market the brand name products eventually fade out creating a vacuum of RLD. At times, it is said that FDA designates one of the ANDA holders, who is the market leader in a given situation, as a new RLD.
- Applicable regulatory guidelines

QTPP define at

- The start of development
- Knowledge gained in development may change some elements

Components of QTPP

Components related to safety, efficacy, identity, purity and potency

1. Critical and non-critical components, e.g.
   - Critical: Assay, content uniformity
   - Non-critical: Appearance
2. Fixed and variable components
   - Fixed elements must be present
     e.g.: Dosage form, strength
   - Variable elements may have a range of acceptable values
     e.g.: Tablet weight, assay

Specific requirements in QTPP

1. Scored tablets
   - Weight variation between two halves
   - Dissolution of half tablet
2. Orally Disintegrating tablets
   - Hardness
   - Disintegration time
   - Container closure
3. Extended-Release products
   - Alcohol induced dose dumping

Critical Quality Attributes (CQAs)

A CQA has been defined as "a physical, chemical, biological or microbiological property or characteristics that should be within an appropriate limit, range, or distribution to ensure the desired product quality." According to ICHQ9 the Identification of CQAs is done through risk assessment. Critical Quality Attributes are associated with the drug substance, excipients, intermediates and drug product. Critical Quality attributes covers the properties that impart the desired quality, safety, and efficacy. In context of biotechnological products, CQAs are typically those aspects which affect product purity and stability. Drug product CQAs can be identified from the QTPP. The use of strong risk assessment methods for identification of CQAs is new to the QbD standard [15, 16].

Critical Material Attributes (CMA) & Critical Process Parameters (CPPs)

Critical material attribute (CMA) and critical process parameters (CPPs) are defined as "A parameters

whose variability have an impact on a CQA and therefore should be monitored or controlled to ensure the process produces the desired quality" Process robustness is the ability of a process to demonstrate acceptable quality and performance and tolerate variability in inputs at the same time. Process capability is a statistical measure of the inherent process variability for a given characteristics. The most widely accepted formula for process capability is six-sigma [17]. Process capability index is the value of the tolerance specified for a particular characteristic divided by the process capability, which is defined as follows:
If the CpK is significantly greater than one, the process is defined capable. But if the process capability is low, there are five step procedures to progressively reduce the variability of the process.

These five steps are:

a) Define: The intended improvement should be clearly stated
b) Measure: The critical product performance attributes should be measured to see if they are out of specification and used to the sigma level of the process.
c) Analyze: When the sigma level is below the target, steps should be taken to increase it, starting by identifying the most significant causes of the excessive variability.
d) Improve: The process should be redesigned and/ or process controls should be incorporated to eliminate or attenuate the significant root causes of variance.
e) Control: The improved manufacturing process should be evaluated and maintained.

Risk Assessment

Risk assessment is the linkages between material attributes & process parameters. It is performed during the lifecycle of the product to identify the critical material attributes & critical process parameters. A material attributes can be an excipients raw material, drug substances, reagents, solvents, packaging & labelling materials. A material attributes can be quantified & typically fixed but sometimes can be changed during further processing [18]. E.g. Impurity profile, porosity, specific volume, sterility.

Formulation by Design (FbD)

Formulation by design (FbD) is a holistic concept of formulation development aiming to design more efficacious, safe, economical and Patient-compliant Drug Delivery System (DDS).

Key Elements of FbD

a) Appropriate choice of Experimental designs
b) Meticulous Drug product development
c) Accurate computer aided optimization

Design and control spaces

ICH Q8 (R2) defines Design space as, the multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated for provide assurance of quality. It will working within the Design space is not be considered as a change, Movement out of the Design space it is considered to be a change and would normally initiate a regulatory post-approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval. Thus Design space is potentially scale and equipment dependent, the Design space determined at the laboratory scale may not be relevant to the process at the commercial scale [19, 20].

It identifies Critical quality attributes (CQAs), Critical formulation attributes (CFAs) and Critical Process parameters (CPPs)

Design of Experiments (DoE)

Design of experiments (DoE) is a systematic method to determine the relationship between factors affecting a process and the output of that process. In other words, it is used to find cause and-effect relationships. This information is needed to manage process inputs in order to optimize the output. An understanding of DoE first requires knowledge of some statistical tools and experimentation concepts. Although a DoE can be analyzed in many software programs, it is important for practitioners to understand basic DoE concepts for proper application [19, 20]. Critical parameters are considered as independent variables in DoE.

DoE is a mathematical tool for systematically planning and conducting scientific studies that change experimental variables together in order to determine their effect on a given response.

DoE makes controlled changes to input variables in order to gain maximum amounts of information on cause-and-effect relationships with a minimum sample size for optimizing the formulation

Types of Experimental Designs

Various type of experimental design methods are available out of which method we have to use depends upon the resources and what we want to study.

a) Screening Designs
b) Response surface Designs

c) Factorial Designs
d) Fractional factorial Design(FFD)
e) Plackett-Burman Designs (Hadamand designs)
f) Central Composite Design(Box-Wilson design)
g) Box-Behnken Designs
h) Taguchi Design
i) Mixture Design

a) **Screening Designs:** To identify important factor and their level which affect the quality of formulation. It supports only the linear responses.
b) **Response surface Designs:** It generally supports non linear and quadratic response and capable of detecting curvatures.
c) **Factorial Designs:** Factorial experiment is one in which all levels of a given factor are combined with all levels of every other factor in the experiment. These are generally base upon first degree mathematical models. FDs can be symmetric or asymmetric based on the levels (same or Different) and factors.
d) **Fractional Factorial Design:** It is mainly used for screening of factor. These designs are economical in terms of number of experiments; the ability to distinguish some of the factor effects is partially sacrificed by reduction in no of experiments.
e) **Plackett-Burman Designs:** To screen high number of factors and some time as high as 7 factors and few dummies are also used. Interpretations of results are drawn with help of Pareto plot.
f) **Central composite Designs:** For nonlinear responses requiring second order models this is preferred. It is popular in response surface optimization during pharmaceutical product development.
g) **Box-Behnken Designs:** It requires only three levels for each factor -1, 0, +1. It employs 15 experiments run with three factors at three levels. It is economical than CCD because it requires less number of trails.
h) **Taguchi Design:** Experimental design as "off line Quality control' because it is a method of ensuring good performance in the development of products or processes.
i) **Mixture Designs:** It is used when the characteristics of the finished product (Drug delivery system) usually depend not so much on the quantity of each substance present but on their proportions.

Software's for Design and Optimization [21].

1) Design Expert
2) ECHIP
3) Multi-simplex
4) NEMRODW
5) Graphpad Prism
6) Software for general statistical nature
7) SAS
8) Minitab
9) SYSTAT

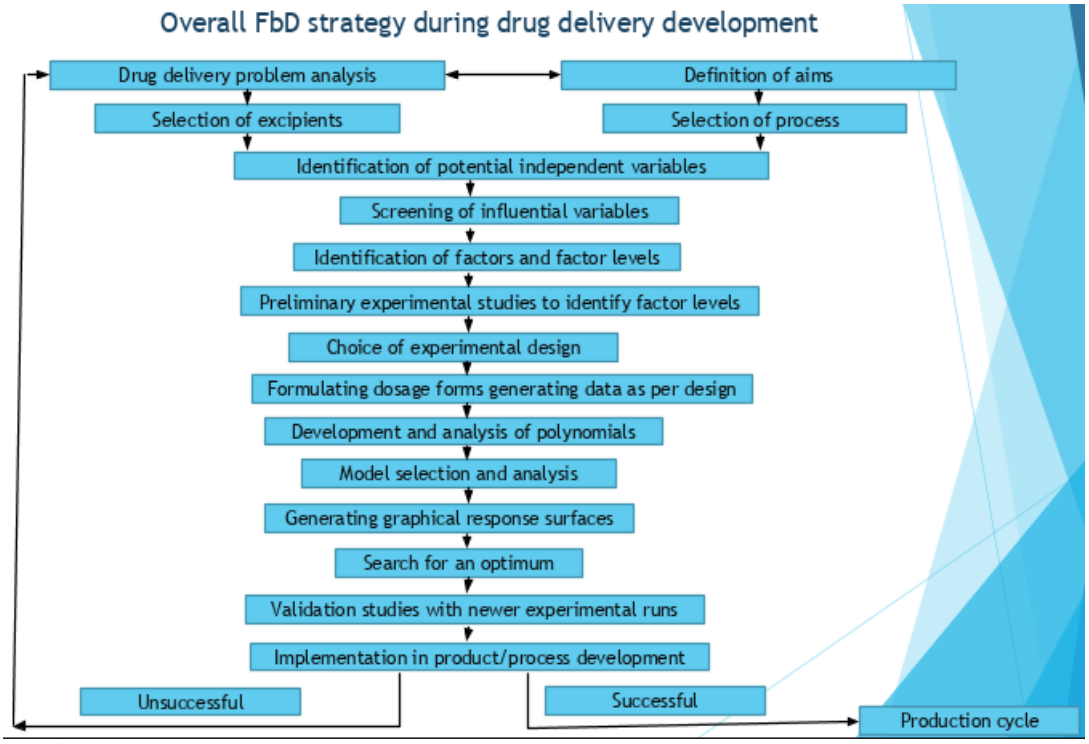
Many commercial software packages are available either dedicated to experimental design alone or are of a more general statistical type.

Overall FbD strategy for Drug delivery Development

Problem definition- FbD problem is clearly comprehended and defined.

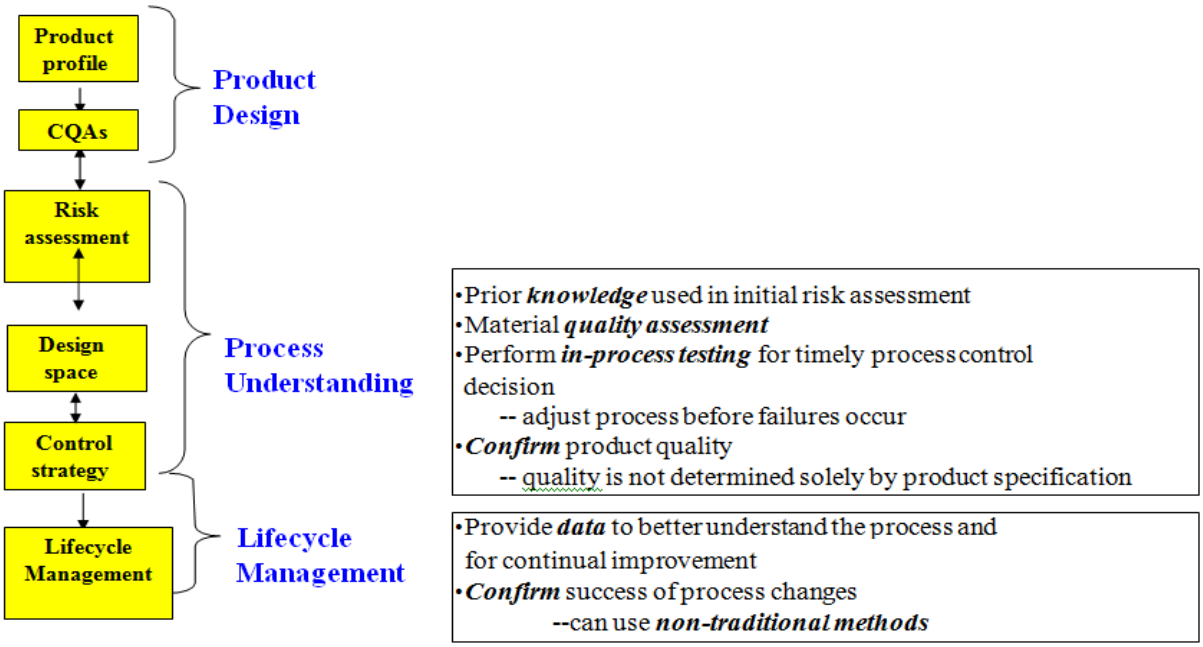
- Selection of Factors and Factor levels- The Independent factors are identified amongst the quantifiable and easy controllable variables.
- Design of Experimental Protocol- Based on the choice of independent factors and the response variables, suitable experimental design is selected and the number of experimental runs calculated.
- Formulating and evaluating the dosage form- Various drug delivery formulations are prepared as per the chosen design and evaluated for the desired responses.
- Prediction of optimum formulation - The experimental data are used for generation of a mathematical model and an optimum formulation is located using graphical or numeric methods.
- Validation of optimization- The predicted optimal formulation is prepared and the responses evaluated. Results, if validated are carried further to the production cycle via pilot plant operations and scale up techniques (Figure 5).

Figure 5: Overall FbD strategy during Drug delivery Development.



Quality by Design Approaches to Analytical Methods- FDA Perspective **(**Figure 6)
A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management- ICH Q8 (R) [22, 23]

Figure 6: Role of Analytical Methods under QbD Paradigm- Provide information about process understanding, process control and product quality



Analytical Method and Risk Management

Risk Factor = Severity x Occurrence x Detectability

- Severity = Effect on Patient
  - Related to safety or efficacy (CQAs)
  - Different than impact of a manufacturing failure
- Likelihood of Occurrence = Chance of Failure
  - Related to product and process knowledge and controls
  - Includes uncertainty for new processes or process changes
- Detectability = Ability to Detect a Failure
  - Appropriateness and capability of analytical method
  - Sampling considerations+

Analytical Method and Control Strategy [24, 25]

Control Strategy Includes:

Process parameters and material attributes related to drug substance and drug product manufacturing Components, facility and equipment operating conditions, In-process controls, finished product specification, and the associated methods and frequency of monitoring and control (Table 3).

Table 3: Use of Analytical Methods in Control Strategy

Raw Material Testing	• Specification based on product QTPP and CQA • Effect of variability, including supplier variations, on process is understood
In process Testing	• Real time (at-, on-, or in-line) measurements • Active control of process to minimize product variation • Criteria based on multivariate process understanding
Release Testing	• Quality attributes predictable from process inputs(Design Space) • Specification is only part of the quality control strategy • Specification based on patient needs (quality, safety, efficacy, performance)
Stability Testing	• Predictive models at release minimize stability failures • Specification set on desired product performance w/time8

Role of Process Analytical Technology (PAT)

- Provide real time information (at-, on- and in-line testing) for process control and improvement
- Non-traditional analytical techniques (e.g. NIR) have been used in these areas:
  - Identification, drying, blending, assay, and content uniformity
- Need reliable reference information to establish calibration models
  - Need to maintain calibration models
  - Sampling effect on model calibration and validation

Analytical Method and Continual Process Improvement

- Routine analysis
  - Provides data for tracking and trending
  - Quantitative results are more useful than PASS/FAIL
- Non-routine analysis
  - Evaluation of product quality on periodic basis for higher quality assurance
  - Reassessment of process or product upon process changes

– Can use non-traditional analytical techniques that are not typically applied to routine release testing

– Performed under firm's quality system

QbD Approach for Analytical Methods [26, 27]

- ICHQ8 (R2) doesn't explicitly discuss analytical method development.
- However, concepts apply (Figure 7, 8):

– Application of Science and Risk based methodology

– Systematic approach that includes: risk assessment, defining a design space, control strategy and continual improvement to increases method robustness and understanding

Figure 7: QbD Approach to Analytical Methods

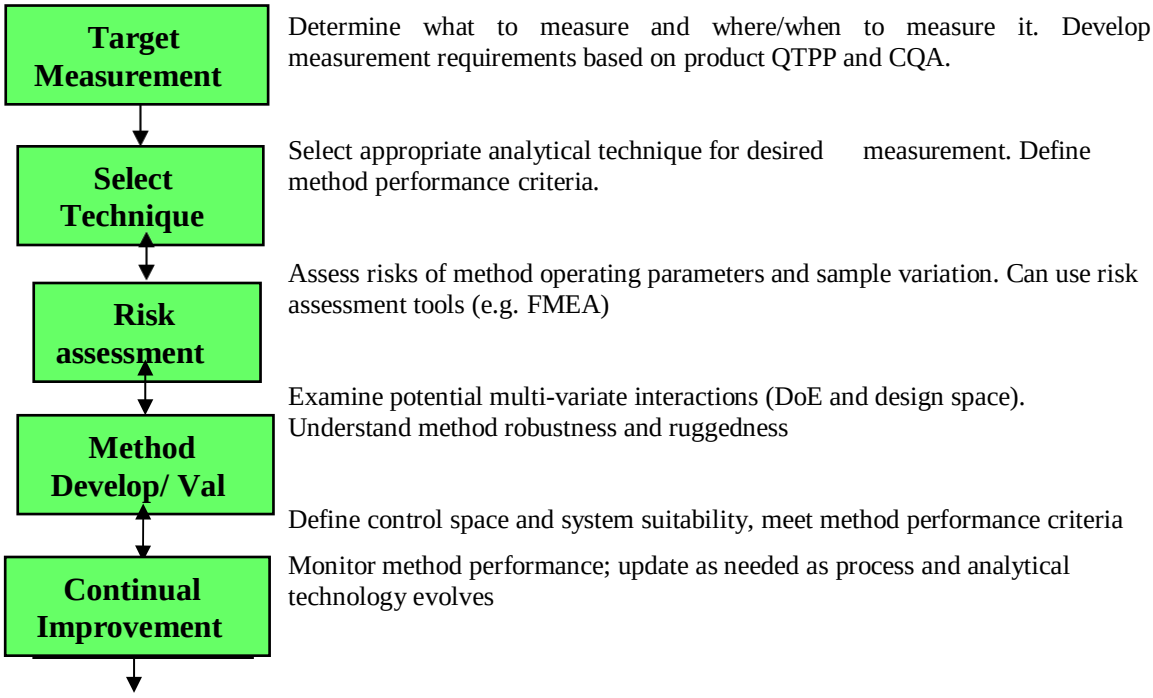
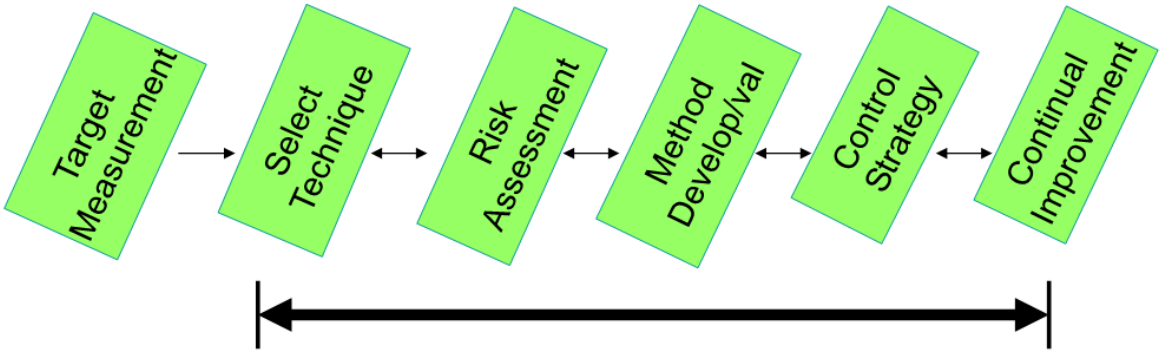


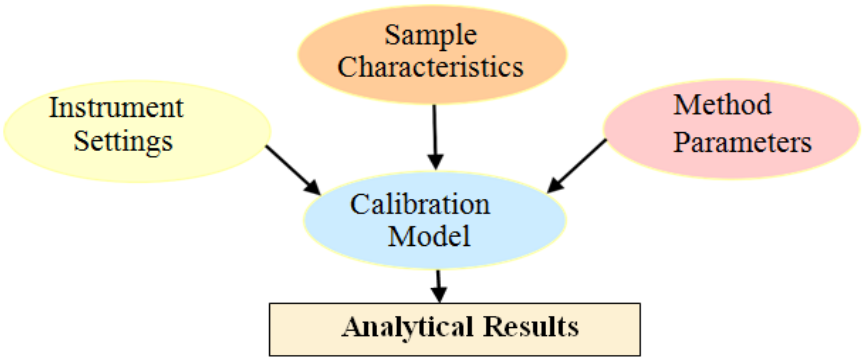
Figure 8: Allow continual feedback and feed-forward interactions among all steps. Meet and maintain method performance criteria



- Many Factors can affect analytical results.

e.g.: variations in instrument, sample, method, choice of model (Figure 9).

Figure 9: Variation of Analytical Method



Analytical Method Understanding

- Understand how variation in input parameters affects analytical results
- Examine multivariate relationships
  - Across instrument, laboratory, analyst, sample and method parameters
- Employ mechanistic understanding
  - Based on chemical, biochemical and physical characteristics
- Incorporate prior knowledge of techniques and methods

Analytical Method "Design Space" [29, 30]

- A science and risk based and multi-variate approach to evaluate effects of various factors on method performance
- Typically, DoE (Design of Experiment) is used to find ranges for instrument operating parameters, to understand sample preparation variations and variations of method precision.
  - Example terminology for design space: MODR (method operable design range)
4. Method performance criteria are response factors
5. Can be conducted together with method validation

Benefits of Application of QbD Approach to Analytical Methods

- Development of a robust method
- Applicable throughout the life cycle of the product
- Regulatory flexibility
  - Movements within "Design Space" are not considered a change in method

Current Status

- FDA has approved some NDA applications applying QbD approach to analytical methods (e.g. HPLC and UV)
- Regulatory flexibility has been granted for movements within the defined analytical method "Design Space"

Regulatory Considerations [31, 32]

- Define intended use of the analytical method (e.g. RTRT (real time release testing) or endpoint testing)
- Not all analytical techniques are inter-changeable
  - Example: from HPLC to NIR
- Require additional development and validation efforts
- Submission of comparability protocols is recommended
- Need sufficient statistical power to support analytical "Design Space"
- Applicants need to clearly define terminologies
- Proposal for regulatory flexibility should consider potential risk to product quality

Process Analytical Technology (PAT)

"A system for designing, analysing, and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality."

Process Analytical Technology (PAT) measurements may be of raw materials, intermediates, and products, and these measurements can provide significant data for understanding how process variables affect chemistry, bioprocess, or particle-based systems.

PAT provides an opportunity to measure previously unknown intermediates, mechanisms, endpoints and can be applied in R&D, Scale-up, and Manufacturing [33-39].

PAT –Areas for Experimentation [40-45]

Insight for Every Experiment

PAT in research and development provides timely measurements that can reveal previously unknown process components and relationships. By collecting data rich experiments researchers gain an in-depth mechanistic insight to every formulation, fermentation, reaction or crystallization. A continuous stream of data throughout an experiment provides a link between process parameters and product quality or downstream process performance. Real-time data means researchers gain immediate insight into each experiment and can make fast, well-informed decisions to improve each subsequent experiment.

Transform Productivity

Researchers map the effect of experiment conditions, collect empirical data to validate predictive models, and gain confidence that a process will safely scale up. Data is collected 24 hours a day to accelerate the knowledge and confidence of each scientist. Process Analytical Technology (PAT) can also be used to provide proof of process understanding regulatory submission documentation.

Improving Laboratory Safety

In situ measurements are often more precise than offline measurements since they avoid the errors caused by sampling and sample preparation. The use of PAT in R&D minimizes personnel hazards associated with sampling hazardous materials for in-process testing especially when working with toxic or corrosive materials or experiments under high pressure.

PAT for Scale-up from Lab to manufacturing [46-48]

Pilot Plant Fault Detection and Optimization

- As a process is scaled up from the lab to pilot plant, PAT can ensure that each step is proceeding as intended. Researchers apply PAT to develop a “signature” or "fingerprint" to monitor process reproducibility during technology transfer. During scale-up, engineers often rely on PAT to verify consistent endpoint in batch processes or steady state operation in continuous processing.
- Inline monitoring provides continuous streams of data which does not require samples to be collected, prepared, and analysed. This enables researchers to make decisions quickly without waiting for offline data.
- The knowledge-rich process information obtained with PAT allows for rapid troubleshooting, optimization, and fault detection. When an unexpected process deviation occurs, PAT can often be used to identify the root cause such as a variation in upstream process conditions, impurities, or raw materials.
- PAT improves safety by providing insight into progress of exothermic reactions, and where sampling may pose operator hazards.

Trouble shooting and Control in Production

Ideally, a process is robust enough that it does not require monitoring when it reaches the manufacturing scale. However, many processes require close monitoring ensure consistency or improve downstream operations, especially when they first reach the manufacturing scale.

PAT applications in manufacturing are often classified in two areas:

a) Knowledge collection to improve the overall robustness of a process, including troubleshooting to identify the root cause of a process deviation;
b) Process control for a batch or continuous process, especially where offline measurements are unstable, infrequent, time consuming, or hazardous.

Often, the return on investment for PAT is clear on the manufacturing scale since elimination of failures, increase in yield, and increase in cycle time can offer significant savings. Considerations of implementing PAT in manufacturing include: safety in a classified explosive environment, chemical compatibility, cGMP requirements, communication with a manufacturing control system, and mounting in with process equipment [49, 50].

Applications of PAT [50, 51]

Process Analytical Technology (PAT) provides key information for a wide range of applications, including:

- Continuous Flow Chemistry
- Crystallization and Precipitation
- Formulations and Product Development
- Fermentation and Bio processing
- PAT for Chemical Reactions

PAT in Tablet manufacturing [52]

Stage	Technique	Measurement
Dispensing	NIR/Raman	Identification of Raw Materials
Wet Granulation	NIR	Moisture Distribution
Drying	NIR	Moisture Content
Blending	NIR	Blend Uniformity
Compression	Strain Gauges	Compression Force
	NIR	Content Uniformity

PAT Examples

Spectral Probe NIR Analyzer installed on viewing window of Glatt FBD without any drying Modification

Real-Time Blend Uniformity by using Tru Process Analyzer

PAT is one of the many tools or enablers of QbD. PAT can be an invaluable tool through life cycle management. During product and process development it can enhance prior knowledge and improve process understanding, help with process mapping and monitoring, model building and along with QRM, help establish a design space and a control strategy. During manufacturing operations PAT can help ensure process robustness and consistent output, as well as enabling operational flexibility through adaptive process controls, based on process understanding, and ultimately Real Time Release (RTR) through a science/risk based approach and Quality Systems. For continual improvement, PAT tools, such as multivariate data analysis and process control systems, enable historical data tracking and trending for continual improvement and consistent patient outcome [53-55].

The concept originates from the desire of the regulators to shift control of product quality towards a science-based approach that explicitly attempts to reduce the risk to patients by controlling the manufacturing based on understanding of the process [56, 57]. From a PAT standpoint, a process is considered well understood when:

a) All critical sources of variability are identified and explained;
b) Variability is managed by the process; and
c) Product quality attributes can be accurately and reliably predicted.

PAT has been defined as "A system for designing, analyzing, and controlling manufacturing through measurements, during processing of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality". The goal of PAT is to "enhance understanding and control the manufacturing process, which is consistent with our current drug quality system: quality cannot be tested into products; it should be built-in or should be by design" [58].

CONCLUSION:

Quality has become an important issue in today's era. Everyone talks on quality but building quality is not mere task. It needs a long process for fulfilment of the required quality attributes in the material. When the term Quality is defined in context of Pharma, it becomes a legal issue. There are numerous guidelines and governing bodies who imply "should be and should not be conditions". Quality by Design and Process analytical technology has been emerging concepts for developing the required quality attributes in the product at its design stage which saves time, energy and also reduces market recall of the products [59, 60].

a) Ensures robust commercial manufacturing methods for consistent production of quality drugs.
b) Ensures the consumers that therapeutic equivalent generics are manufactured every single time.
c) Offers the agency that quality applications are submitted to improve the review efficiency and to reduce the application approval times.
d) QbD methodology helps in identifying and justifying target product profiles, product and process understanding.
e) Helps in continuous improvement.
f) There is a need for vigorous and well-funded research programs to develop new pharmaceutical manufacturing platforms.

Analytical techniques and methods play an essential role in QbD paradigm. Real time release testing and non-traditional testing techniques provide valuable information for in-process control and improvement. Regulatory flexibility is achievable by applying QbD approach, but requires high degree of process, product and analytical method understanding and robust quality systems. Applicants are encouraged to discuss 'novel' QbD implementation approaches with the agency prior to submission.

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