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Commentary Article

QUALITY IMPROVEMENT WITH SCIENTIFIC APPROACHES (QBD, AQBD AND PAT) IN GENERIC DRUG SUBSTANCE DEVELOPMENT: REVIEW

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ABSTRACT

Drug substance synthesis requires strong chemistry knowledge and innovative thinking to publish and challenge patents. Creative synthetic route supports to have critical patent claims and challenges the entry of generic players in the market. Since innovators are covering many parameters like stereo selective (isomerism), polymorphic (crystallinity), salt or ester form, impurity profile apart from residual solvents, chemicals and reagents in their patents, drug substance synthesis is a big challenge to the generic manufacturers. Generic drug manufacturers target is to develop a simple and cost effective synthetic route to meet the market competition from other players. Drug substance development can be employed with two approaches traditional and/or scientific approaches. Traditional approach progressed with previous knowledge, reactions reproducibility, less experimental data when compared with scientific approach. In recent years all regulatory agencies are recommending to follow scientific approach rather than traditional approach. Scientific approach can be employed with scientific tools such as quality by design (QbD), analytical quality by design (AQbD) and process analytical technology (PAT) for process development and manufacturing. These three tools will provide enough understanding on drug development and manufacturing. Authors have discussed about quality improvement with scientific approaches.
Keywords: Drug substance synthesis; Quality by design (QbD); Analytical QbD (AQbD); Process analytical technology (PAT); Scientific approach; Risk assessment; Impurity profile.

INTRODUCTION

The discovery of a drug substance depends on good scientific knowledge. Drug discovery life cycle has three phases' discovery, clinical trials and selection of route of administration. Discovery synthetic route and synthetic process development of a new drug entity (NDE) or new chemical entity (NCE) becomes more difficult and expensive due to increasing stringent regulations (patents and exclusivity) and scientific applications [1-6]. Generic Drug substance synthesis is a challenge due to patents coverage on stereo selective (isomerism), particle size and polymorphic (crystallinity), salt or ester forms [7-11], impurity profile and residual solvents. Final drug substance (active pharmaceutical ingredient-API) should have therapeutic use and biologically active, safe and scale up the batch sizes for safety and clinical trials. Discovery of new drug substances can be achieved by extraction or synthetic or semi synthetic

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processes. Extraction from natural or biological source includes complex process and yields final product with less productivity. High yields can be achieved with synthetic process. Preferably, Small molecules are preferable for oral drug administration and organic synthesis is required to modify natural compounds. Drug substance synthesis and manufacturing can be processed either traditional or scientific approaches. Scientific approach follows with full understanding on product synthesis, analysis and risk assessment but traditional approach follows with reproducibility and previous knowledge. In recent years all regulatory agencies are recommending to use scientific tools in drug substance synthesis and drug product manufacturing. Scientific tools includes quality by design (QbD), analytical quality by design (AQbD) and process analytical technology (PAT) for development and manufacturing of drug substance synthesis and drug product formulation. Understanding of these three approaches will provide knowledge of development and manufacturing [12,13]. The chemical synthesis in new drug development has vital importance. It depends on the molecule structure, physical and chemical properties. Complexity of the synthesis increases with number of functional groups and their arrangement in the molecule. If chemical structure has chiral center then more focus is required on synthetic process and controls. Physical properties such as polymorphism, hygroscopicity, photo sensitivity, particle size and physical stability will determine the synthetic process criticality. Chemical properties such as impurity profile, degradation pathways, metabolites formation and chemical stability are important in the synthetic route selection and process. Regulatory requirements are increasing gradually to maintain high quality. These all factors are directly influencing the cost of new drug development and manufacturing [14,15]. ICH quality guidances Q8-Q11 has discussed about pharmaceutical development, scientific approaches implementation and control of materials [16-19]. In this review, authors have discussed about traditional and scientific approaches in drug substance synthesis and how the product quality improves with scientific approaches implementation (QbD, AQbD and PAT).

Traditional approach

Traditional approach can be progressed with synthetic route strategy, practically execute the synthetic route, repeatability in lab scale, pilot scale, pivotal scale (exhibit batch) and commercial scale. Figure 1 represents the drug substance synthesis in traditional approach.

Synthetic route strategy

This is the initial phase of API synthesis. This includes understanding of molecule properties, literature search for synthetic route, patents search, challenges in novel synthetic route; starting material selection.

Practically execute the synthetic route

In this phase scientist will execute the complete synthetic process (all steps) in the laboratory. All synthetic stage products (intermediates) and bi-products will be characterized with analytical techniques such as spectroscopy (UV/Visible, FT-IR, NMR and Mass) and chromatography (HPLC, GC, TLC and IC). The information obtained from these results definitely will be useful to define the in-process and finished product impurity profile [20-22] and specification limits.

Repeatability in lab scale

Scientist will execute the same quantity synthetic reactions in the same laboratory for repeatability evaluation and finalize the specifications and analytical test procedures to progress method validation and method transfer activities. In this step both synthetic and analytical scientists should ensure and understand the pilot scale requirements.

Pilot scale

Research team will synthesize all steps with pilot scale quantities and understand the requirements and changes for pivotal scale (Exhibit batch). The pilot scale batches will be repeated with incorporation of changes required if any.

Pivotal scale (Exhibit batch)

This step should be completed in GMP (good manufacturing practices) area. All analytical procedures for raw materials, in-process and finished products will be transferred to quality control laboratory by performing method transfer/verification. In general minimum three process validation batches will be manufactured and monitored. Process validation protocol/report can be prepared for these three exhibit batches.

DMF submission

All three exhibit batches will be charged for stability studies in accelerated, intermediate and long term storage conditions. After completing six month stability time interval DMF will be prepared as per the regulatory requirements (ICH, USFDA or EMA, etc.) and submitted for agencies approval [23-29].

Commercial scale

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Process validation batches will be manufactured with approved manufacturing and analytical procedures. All post approval activities including manufacturing, storage, stability [30-33], logistics and CMC (chemistry, manufacturing and control) changes will be handled as per the agencies GMP (good manufacturing practices) and GDP (good distribution practices) requirements [34-43].

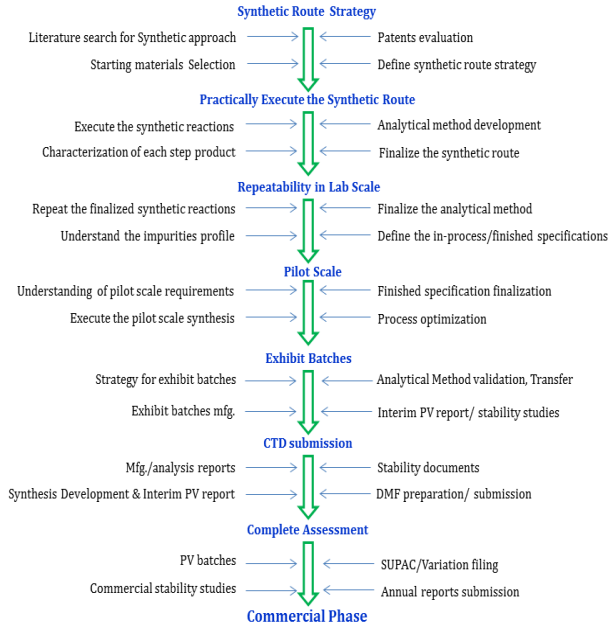

Figure 1: Drug substance synthesis in traditional approach.

Scientific approaches (QbD, AQbD, PAT)

Quality by design (QbD)

In a traditional approach, finalization of synthetic route is based on demonstration of synthetic process reproducibility and acceptance criteria. In QbD approach, risk management and scientific knowledge are used to identify and understand process parameters and unit operations that impact quality attributes. QbD can develop a high quality product with enough understanding on product development, risk assessment and statistical data. QbD key elements are QTPP, CQA, CMA, CPP, DoE, DS, CS and CPM. These QbD tools can apply equally to synthetic development and manufacturing process [44-48]. Figure 2 shows the QbD approach for drug substance synthesis.

Quality target product profile (QTPP)

QTPP is used to select the targeted final product quality attributes such as starting material, synthetic route steps, impurity profile [49-56], polymorphic form, isomeric form, residual solvents and specification limits. ICH Q8 guidance defined as "A prospective summary of the quality characteristics of a drug product that ideally will be achieved

Figure 2: Drug Substance synthesis in QbD approach.

to ensure the desired quality, taking into account safety and efficacy of the drug product".

Critical quality attributes (CQA)

Quality attributes are divided in to low, medium and high risk quality attributes. High risk quality attributes are considered as critical quality attributes (CQA). Drug substance CQAs normally includes organic impurities [57-60] (including potentially mutagenic impurities), inorganic impurities (metal residues and residual solvents), purification, crystallization, isomerization, polymerization and stability. If physical properties are important with respect to medicinal product manufacture or drug delivery, these can be considered as CQAs. All CQAs risk can be minimized with developmental experiments and progressed further.

Critical material attributes (CMA)

These are starting materials, reagents, solvents, process aids, intermediates; by-products, carryovers etc. All CMAs should be identified based on the understanding of designed and

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executed synthetic route. All materials attributes are categories as low, medium or high risk attributes. All these high risk attributes are considered as CMA and risk assessment can be performed as like CQA and minimized with developmental experiments.

Critical process parameters (CPP)

Each synthesis step process parameters can be understood to define the CPP. Synthetic step may be reaction or purification or purging or salt formation. Laboratory executed experiments are the base for defining the CPP for whole synthetic process. As like CQA and CMA classification CPP can be categorized such as low, medium and higher risk process parameters. Further experimental studies such as DoE progressed to determine the significance of individual variables and potential interactions. Once the significant parameters are identified, further studies performed through DS and CS to achieve a higher level of process understanding.

Design of experiments (DoE)

DoE experiments are used to evaluate the impact of the CQA, CMA and CPP variables to gain greater understanding of the process and to develop a proper design space and control strategy. DoE can define all critical factors such as temperature, time, pressure, reagents and rate of addition, catalyst, solvent, concentration and pH such as temperature, time, pressure, reagents and rate of addition, catalyst, solvent, concentration and pH, that can influence the yield, purity and selectivity.

Design space (DS)

Design space can be used during development to identify those impacts potential synthetic process. Further risk assessments can be used for better understanding of the link between process and quality attributes. DoE tool used for determination of appropriate design space between material specifications and process parameter ranges.

Control strategy (CS)

Control strategy includes an assessment of manufacturing process capability; analytical procedures intended ability, attribute detectability and impact of drug substance quality. The risk related to impurities can be controlled by specifications for raw material/intermediates and robust purification capability in downstream steps. It is important to understand the each synthetic stage reaction and purge (whether the impurity is removed via crystallization, extraction, etc.) as well as their relationship with drug substance CQAs. The process should be evaluated to establish appropriate controls for impurities as they progress through multiple synthetic process operations.

Continuous process monitoring (CPM)

CPM is used to monitor the manufacturing process after development and it is continuous process. CPM is used to pre-identify the risk and minimize the risk with supporting experiments and control strategy. CPM is executed along with CMM (continuous method monitoring) by using process analytical technology (PAT).

Analytical quality by design (AQbD)

AQbD is used to develop a unique analytical procedure for qualitative and quantitative determination of analytes. AQbD is similar approach as like QbD. AQbD tools are ATP (analytical target profile), CQA (critical quality attributes) with risk assessment, CMA (critical method attributes), MODR (method operational design region), Control strategy, AQbD method validation and CMM (continuous method monitoring) [61-65]. Figure 3 represents the AQbD approach for analytical method development in drug substance synthesis.

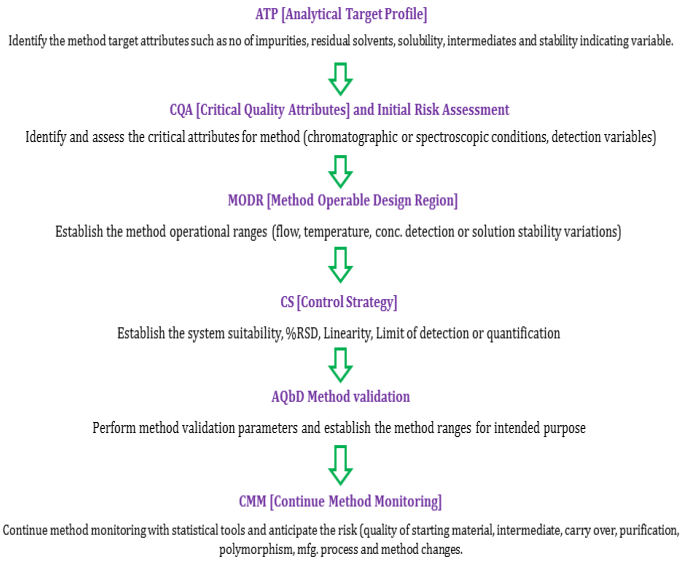

Figure 3: Analytical method development with AQbD approach.

Analytical target profile (ATP)

ATP is used to define the method performance goals and acceptance criteria. Generally, ATPs are determined based on the drug synthetic reaction, starting materials, impurities profile, by products, reaction additives etc. Analytical techniques can be varied based on the chemical nature of the analytes. ATP

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may vary from one procedure to another which means that assay method requirements and impurity profile are different.

Critical quality attributes (CQA) and initial risk assessment

All defined quality attributes should be categorized in to three types like low, medium and high risk attributes. Developmental experiments executed to understand all CQAs and minimize the risk.

Method operational design region (MODR)

Developmental experiments should be performed to understand and define the method operational conditions and ranges. MODR will define the design space for each parameter in the proposed method to assure the method accuracy and precision.

Control strategy (CS)

CS is used to establish the acceptance criteria for method operational conditions, method suitability and allowable ranges. CS will assure the method performance and product quality including method parameters and attributes, components, facility and equipment operating conditions and raw materials, in-process, finished product quality.

AQbD method validation

MODR and CS steps will provide the enough information via experimental and statistical data. Method validation progressed for all parameter such as specificity, accuracy, precision, robustness, linearity, LOQ/LOD [66-71]. Method validation performed with different batch samples and standard materials. Method transfer should be progressed from research laboratory to manufacturing laboratory [72-76].

CMM (Continuous method monitoring)

It is continuous process throughout the after the product approval. CMM is used to monitor the analytical method parameters and CPM is used to monitor the manufacturing process these both will be monitored with PAT execution. CMM will anticipate the risk and alarm the requirement to change the method for intended purpose.

PAT (Process analytical technology)

PAT can be interpreted by using statistical tools in a scientific manner. Many perceptions on PAT like mathematical, chemical, regulatory and production. PAT will improves the manufacturing productivity across all firms like API, drug product, medical device etc. In general, PAT has four stages such as

1. Process understanding
2. Principles and tools
3. Strategy for implementation
4. Execution [77-80].

Stage-1: Process understanding

Drug substance synthetic route may have multi step reactions and each step should be clearly understand such as reaction process, addition of reactants, catalysts, solvents or reagents, by-products, carryovers and rearrangement. PAT will anticipate the source of variable attributes such as material quality, manufacturing process and equipment and manufacturing controls. PAT needs high degree of process understanding to maintain the high quality.

Stage-2: Principles and tools

PAT principles and tools are introduced during the process development stage. The advantage of introducing these principles and tools in development phase is to create possibilities to improve the manufacturing and analysis process for establishing high quality standards. PAT has several tools to understand manufacturing process for scientific, risk-based pharmaceutical development, manufacture and product quality assurance. These tools can be used for process understanding, continuous improvement and development of risk minimization approaches. PAT tools are categorized as

1. Multivariate Data Analysis (MVDA)
2. Monitoring
3. Process controls
4. DoE
5. Chemo metric measurements and
6. Quality control cards.

Stage-3: Strategy for implementation

PAT implementation strategy can be defined based on product manufacturing and analysis understanding.

Stage-4: Execution

Execution of PAT is a continuous process. It helps to improve the product quality with consistency. If any pre identified changes or quality issues are there, then those all should be assessed. Figure 4 represents the PAT tools for drug substance synthesis and manufacturing.

Traditional and scientific approaches (QbD, AQbD and PAT)

API life cycle can be divided in to six stages such as initiation, lab scale, lab to pilot scale, pilot scale, exhibit batch and commercial (production). Figure 5 represents API life cycle

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stages with traditional and scientific approaches QbD, AQbD, PAT.

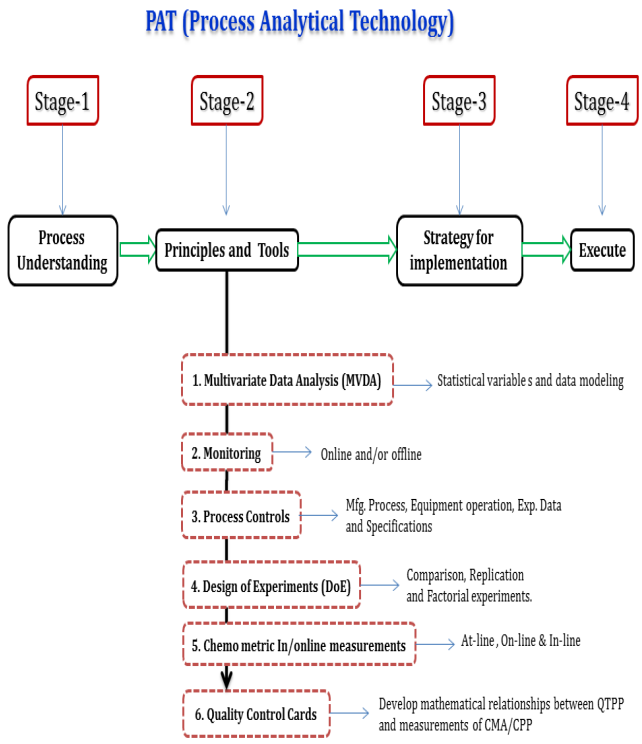

Figure 4: PAT approach for drug substance manufacturing.

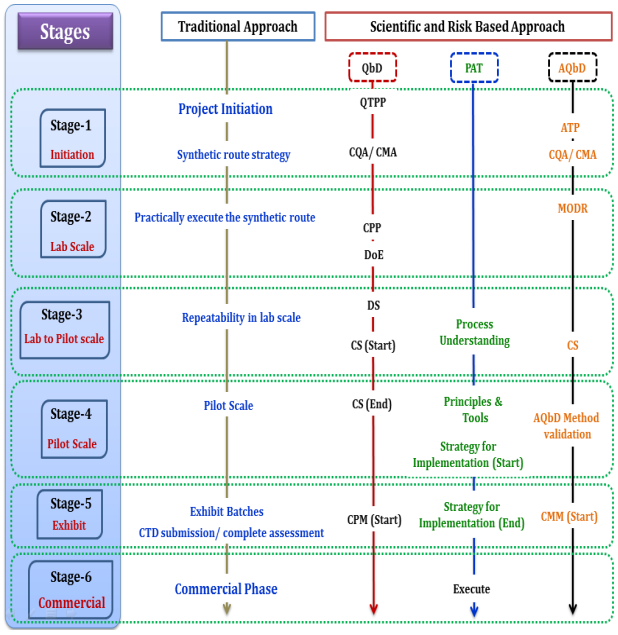

Figure 5: Drug substance life cycle stages (comparison of traditional and scientific-risk based appraoches).

Traditional and scientific approaches have differences in product understanding, risk identification, operational and manufacturing process parameter ranges, control strategy and final product quality. Key considerations are discussed below,

1. Scientific approaches follow risk based design space (DS) establishment with combination of prior knowledge, understanding of chemical structures and synthetic process.
2. DS should be determined for each unit of operation such as reaction, crystallization, distillation and purification etc.
3. The chain between each synthetic step should be evaluated. This helps the control on generation of impurities and improves the quality.
4. In traditional approach, starting material (SM) can be selected by considering specifications but in scientific approach, API manufacturer will evaluate the SM synthetic process, impurity profile and specifications. This can influence to identify and anticipate the impact of SM in total API synthetic route and impurity profile.
5. Impurities can be removed in purification operations (e.g., washing, crystallization of isolated intermediates). This reduces the impurities carry over to the final stage.
6. Scientific approach provides extra assurance on determination of material attributes, risk management and synthetic process understanding.
7. The concept of control strategy was not widely applied in case of traditional approach whereas the scientific and risk based approaches demands to have control strategy in place to ensure product robustness with consistent quality.
8. Scientific and risk based approaches would additionally include the following elements
    a) Product understanding, Risk Evaluation and refining all quality attributes.
    b) Pre-identification of risk attributes (developmental, manufacturing, operational, etc.).
    c) Defining CMA such as raw materials, starting materials, reagents, solvents, process aids and intermediates.
    d) Determining the functional relationships among material attributes and process parameters.
9. In a traditional approach, synthetic process parameters can be fixed with narrow acceptable

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ranges based on reproducibility results whereas in scientific approaches by studying DoE and DS experiments.

10. In traditional approach, scientists have limited flexibility in the operating ranges to address variability of raw materials, reaction process and operation parameters but in scientific approaches it is systematic. This allows scientists to develop and manufacture a high quality product.
11. PAT can be used to enhance the control on manufacturing process and maintain consistent high quality at the end.
12. Quality risk management (QRM) can be applied in all stages during development and manufacturing. QRM used to guide and justify development decisions (e.g., risk assessment and functional relationships linking material attributes and process parameters to API CQAs).
13. Changes within the design space aren't considered as a change. Movement out of the design space is considered to be as a change and all these changes should be handled as per regulatory guidelines.
14. Manufacturing process performance and effectiveness of control strategy should be periodically evaluated and gained knowledge can be applied to improve product quality.
15. Any proposed change should be evaluated for the impact on the quality of final API. This evaluation should proceed based on scientific understanding of the manufacturing process and parameters.
16. Extension of ranges for lower risk parameters does not require prior regulatory approval, although notification may be called for depending on regional regulatory requirements and guidance.

SUMMARY

Traditional approach performs the control strategy for manufacturing process and operating ranges on the basis of process reproducibility and established acceptance criteria but scientific approach performs with enough understanding on process parameters and unit operations. Scientific approach would additionally provide assurance on quality attributes, pre-identification of risk attributes (developmental, manufacturing, operational etc.) and defined the material attributes such as raw materials, starting materials, reagents, solvents, process aids and intermediates. Scientific approaches will be employed with risk basis which produce the high quality product with consistency yield. All regulatory bodies are encouraging to follow scientific approaches such as QbD, AQbD and PAT for drug substance synthesis.

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