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Review Article

Analytical Quality by Design Approach to Test Method Development and Validation in Drug Substance Manufacturing

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Pharmaceutical industry has been emerging rapidly for the last decade by focusing on product Quality, Safety, and Efficacy. Pharmaceutical firms increased the number of product development by using scientific tools such as QbD (Quality by Design) and PAT (Process Analytical Technology). ICH guidelines Q8 to Q11 have discussed QbD implementation in API synthetic process and formulation development. ICH Q11 guidelines clearly discussed QbD approach for API synthesis with examples. Generic companies are implementing QbD approach in formulation development and even it is mandatory for USFDA perspective. As of now there is no specific requirements for AQbD (Analytical Quality by Design) and PAT in analytical development from all regulatory agencies. In this review, authors have discussed the implementation of QbD and AQbD simultaneously for API synthetic process and analytical methods development. AQbD key tools are identification of ATP (Analytical Target Profile), CQA (Critical Quality Attributes) with risk assessment, Method Optimization and Development with DoE, MODR (method operable design region), Control Strategy, AQbD Method Validation, and Continuous Method Monitoring (CMM). Simultaneous implementation of QbD activities in synthetic and analytical development will provide the highest quality product by minimizing the risks and even it is very good input for PAT approach.

1. Introduction

Pharmaceutical industry has focused on product Quality, Safety, and Efficacy. Product quality has been increasing by implementing scientific tools such as QbD (Quality by Design) and PAT (Process Analytical Technology). Scientific approaches will provide the clear and sufficient knowledge from product development to manufacturing. These QbD tools will minimize the risk by increasing the productivity and quality. Nowadays QbD approach has been successfully implemented in generic formulation development. USFDA has released specific QbD guidance for immediate and extended release drug products. Regulatory authorities are always recommending the implementation of ICH quality guidelines Q8 to Q11 [1–4].

Analytical Quality by Design (AQbD). As per ICH, QbD is defined as "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."

Equivalent to process QbD, the outcome of AQbD is well understood and fit for intended purpose with robustness throughout the lifecycle. AQbD life cycle has different tools such as ATP (Analytical Target Profile), CQA [5, 6], Risk Assessment, Method Optimization and Development with DoE, MODR (method operable design region), Control Strategy and Risk Assessment, AQbD Method Validation, and Continuous Method Monitoring. Figure 1 represents the AQbD life cycle with each tool.

Scientific QbD Approach for Synthesis and Analysis. ICH Q11 has explained the QbD approach for API synthetic process development but there is no specific discussion on AQbD. However, it is recommended to implement QbD approach in analytical method development termed as AQbD. These two

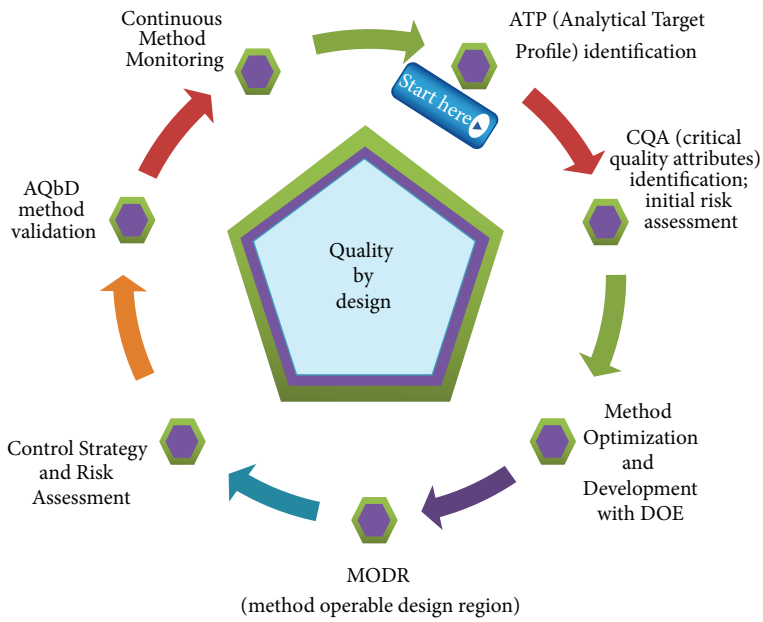

Figure 1: AQbD tools and life cycle.

Table 1: QbD tools for synthetic development and analytical development.

Steps	Synthetic development (QbD)	Analytical development (AQbD)
1	QTPP identification	ATP (Analytical Target Profile) identification
2	CQA/CMA identification, Risk Assessment	CQA identification, Initial Risk Assessment
3	Define product design space Define process design space	Method Optimization and development with DOE
4	Refine product design space	MODR (Method Operable Design Region)
5	Control Strategy with Risk Assessment	Control Strategy with Risk assessment
6	Process validation	AQbD Method Validation
7	Continuous process monitoring	Continuous Method Monitoring

scientific approaches (QbD and AQbD) can be progressed in equal time. Figure 2 represents the necessary steps in API synthesis and analytical development with QbD implementation. This simultaneous implementation produces high quality product. It may give better input for initiation of process analytical technology (PAT).

The expression of tools in QbD and AQbD is different for synthetic development and analytical development. Both QbD and AQbD tools are presented in Table 1.

Differences for Traditional and Scientific Approach. Analytical method development traditional and scientific approaches have large difference. Traditional approach does not use statistical calculations and risk assessment. AQbD approach will proceed with scientific tools such as ATP, CQA, DoE and Risk Assessment, Control strategy and Risk Assessment and AQbD Method Validation, and Continuous Method Monitoring. Figure 3 represents the steps for traditional and scientific approaches for analytical development.

2. ATP (Analytical Target Profile)

ATP [7, 8] identification includes the selection of method requirements such as target analytes (product and impurities), analytical technique category, and product specifications. Initial risk assessment would be performed for anticipation of the method requirements and analytical criticalities. General ATP for analytical procedures is as follows:

(a) target analytes selection (API and impurities),

(b) technique selection (HPLC, GC, HPTLC, Ion Chromatography, chiral HPLC, etc.),

(c) method requirements selection (assay or impurity profile or residual solvents).

Example. A model synthetic route is presented in Figure 4 with ATP impurities. This synthetic route has been considered for analytical method development by HPLC/UPLC, HPTLC, or GC techniques with AQbD implementation. DS synthetic route has eight steps from the starting material. Additional new raw materials are added at stages 4 and 6. Byproducts are forming at stages 5 and 7. Stage 4 product is a degradation of final drug substance. Stage 6 is a carryover to final DS.

(a) Target Analytes Selection. ICH Q3 and all other regulatory guidance explained the consideration of impurities in the API

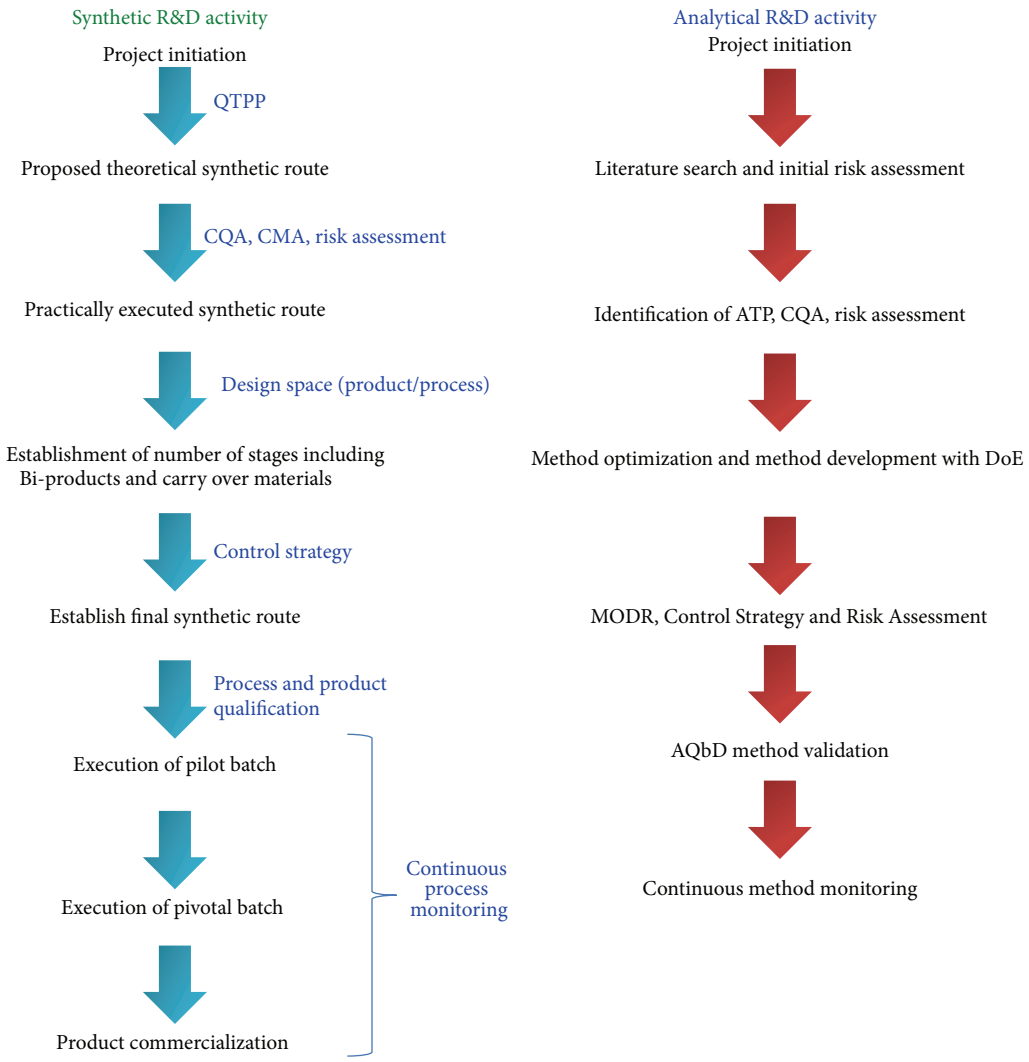

Figure 2: API synthetic development and AQbD approach.

synthetic route. Based on the above synthetic route (Figure 4), analytical target profile (ATP) impurities are as follows:

(1) *starting material:* it is starting material for DS;

(2) *stage 4 product:* it is final DS degradation product;

(3) *material-1:* it is new addition material in stage 4 for formation of stage 5;

(4) *material-2:* it is new addition material in stage 6 for formation of stage 7;

(5) *Bi-product-1:* it is byproduct for stage-6;

(6) *Bi-product-2:* it is byproduct of final DS;

(7) *stage-6 product:* it is carryover material in the formation of final DS;

(8) *stage-7 product:* it is reactant in final DS/penultimate to final DS.

(b) Technique Selection. Each analytical technique has specific principle so based on the analytes nature it can be selected. However, analytical test item and purpose of test are also important for selecting the technique. Analytical test items and analytical techniques are as follows:

(1) identification by IR: FT-IR spectrophotometer,

(2) impurity profile (Chromophore): HPLC with UV detector,

(3) impurity profile (non-Chromophore): HPLC with RID/ELSD and so forth,

(4) assay by HPLC (Chromophore): HPLC with UV detector,

(5) assay by HPLC (non-Chromophore): HPLC with RID/ELSD and so forth.

(c) Method Requirements Selection. Method requirements can vary from one method to another. The common ATPs for impurity profile by HPLC method are listed in Table 2.

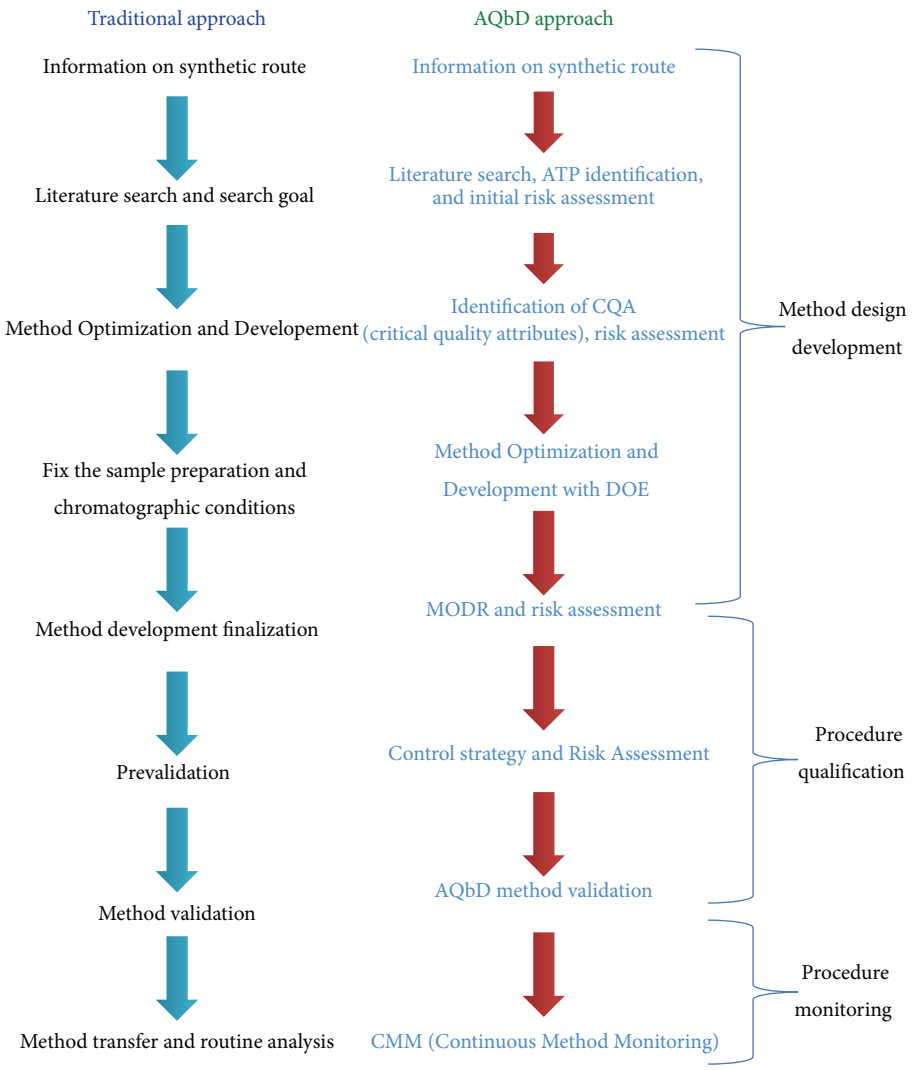

Figure 3: Traditional and AQbD approach for analytical method development.

3. CQA (Critical Quality Attributes) and Initial Risk Assessment

(i) CQA (Critical Quality Attributes). CQA for analytical methods includes method attributes and method parameters. Each analytical technique has different CQA. HPLC (UV or RID) CQA are mobile phase buffer, pH, diluent, column selection, organic modifier, and elution method. GC methods CQA are gas flow, oven temperature and program, injection temperature, sample diluent, and concentration. HPTLC method CQA are TLC plate, mobile phase, injection concentration and volume, plate development time, color development reagent, and detection method. Nature of impurities and DS can define the CQA for analytical method development such as solubility, pH value, polarity, charged functional groups, boiling point, and solution stability. Table 3 represents the common ATPs and CQA for an HPLC method.

(ii) Risk Assessment. Risk Assessment is a science-based process used in quality risk management and it can identify the material attributes and method parameters (ATP). Risk Assessment can be performed from initial stage of method development to continuous method monitoring. AQbD approach involves the risk identification at early stages of development followed by appropriate mitigation plans with control strategies that will be established. In general, Ishikawa fishbone diagram can be used for risk identification and assessment. See Figure 5 that shows fishbone risk identification approach for typical analytical test procedure.

4. DoE: Design of Experiments (Method Optimization and Development) [9]

Once the potential and critical analytical method variables are defined with initial risk assessment, then DoE can be performed to confirm and refine critical method variables

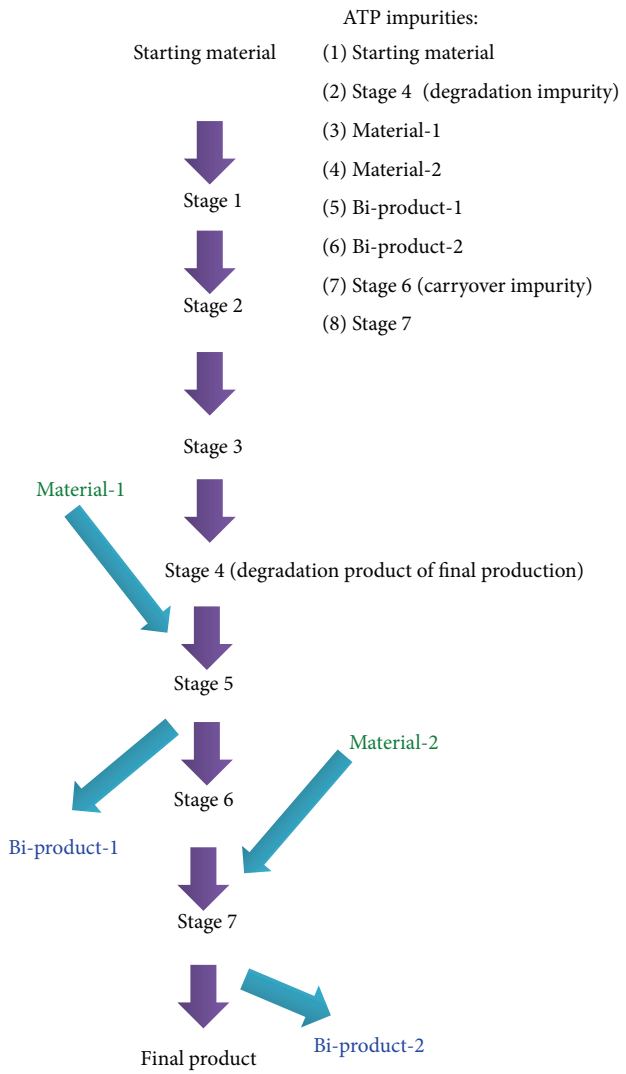

Figure 4: Analytical QbD (AQbD) relation with synthetic development.

based on statistical significance. It can be determined per unit operation or combination of selected multiple method variables and their interactions and responses (critical method attributes). This approach provides an excellent opportunity to screen a number of conditions generated from a limited number of experiments. Then, data evaluations by using statistical tools are very important to identify critical method variables and the appropriate optimal ranges for method variables where a robust region for the critical method attributes could be obtained.

As per ICH Q8 guidance process robustness is defined as "Ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality." Starting materials properties will affect the drug substance synthetic process robustness, impurity profile, physicochemical properties, process capability, and stability. Process understanding will provide the sufficient knowledge for establishing robustness parameters by evaluating different operating conditions, difference scales, and different equipments.

Table 2: Common ATPs for impurity profile by HPLC method.

Serial number	Method requirements for impurity profile
1	Number of analytes (API and impurities)
2	Separation of all analytes
3	Mobile Phase (buffer and organic modifier)
4	Elution method (gradient or isocratic)
5	Sample concentration
6	Sample diluent
7	Sample solution stability
8	Sample preparation process (dilution process and sonication time, etc.)
9	Filter or centrifuge
10	Impurity specification limits
11	Column type (stationary phase and dimensions)
12	Detection (UV/RID/ELSD)
13	RRT, RRF establishment
14	Flow rate
15	Injection volume
16	Column oven temperature
17	Runtime
18	System suitability parameters selection with limits
19	LOD and LOQ concentrations establishment
20	Impurities calculation method
21	Recovery establishment

5. MODR (Method Operable Design Region)

Method operable design region (MODR) is used for establishment of a multidimensional space based on method factors and settings; MODR can provide suitable method performance. It is also used to establish meaningful method controls such as system suitability, RRT, and RRF. Further method verification exercises can be employed to establish ATP conformance and ultimately define the MODR.

6. Control Strategy and Risk Assessment

Control strategy [10–13] is a planned set of controls, derived from analyte nature and MODR understanding. Method control strategy can be established based on the complete statistical data collected during the DoE and MODR stages as discussed above. Using this statistical experimental data, correlations can be drawn between method and analyte attributes for the ability to meet ATP criteria. Control strategy will resolve the method parameters inconsistency (e.g., reagent grade, instrument brand or type, and column type). Method control strategy does not appear dramatically different under the AQbD approach when compared to the traditional approach. However, method controls are established based on CQA, DoE, and MODR experimental data to ensure a stronger link between the method purpose and performance.

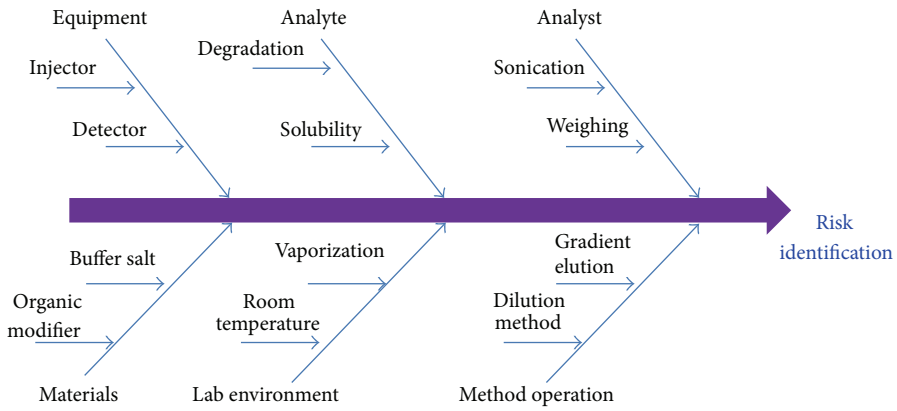

Figure 5: Fishbone for Risk identification.

Table 3: Common ATPs for impurity profile by HPLC method.

Serial number	Analytical Target Profile (ATP)	CQA with Risk Assessment		
		Low	Medium	High
1	Number of analytes (API and impurities)			√
2	Separation of all analytes			√
3	Mobile Phase (buffer and organic modifier)			√
4	Elution method (gradient or isocratic)			√
5	Sample concentration			√
6	Sample diluent			√
7	Sample solution stability		√	
8	Sample preparation process (dilution process and sonication time, etc.)		√	
9	Filter or centrifuge		√	
10	Impurity specification limits			√
11	Column type (Stationary phase and Dimensions)			√
12	Detection category (UV/RID/ELSD)		√	
13	RRT, RRF establishment		√	
14	Flow rate	√		
15	Injection volume	√		
16	Column oven temperature		√	
17	Runtime		√	
18	System suitability parameters selection with limits		√	
19	LOD and LOQ concentrations establishment			√
20	Impurities calculation method establishment			√
21	Recovery establishment			√

7. AQbD Method Validation

AQbD [14–23] method validation approach is the validation of analytical method over a range of different API batches. It uses both DoE and MODR knowledge for designing method validation for all kinds of API manufacturing changes without revalidation. The approach provides the required ICH validation elements as well as information on interactions, measurement uncertainty, control strategy, and continuous improvement. This approach requires fewer resources than the traditional validation approach without compromising quality.

8. Continuous Method Monitoring (CMM) and Continual Improvement [24–30]

Life cycle management is a control strategy used for implementation of design space in commercial stage. CMM is final step in AQbD life cycle; it is a continuous process of sharing knowledge gained during development and implementation of design space. This includes results of risk assessments, assumptions based on prior knowledge, statistical design considerations, and bridge between the design space, MODR, control strategy, CQA, and ATP. Once a method validation is completed, method can be used for routine purpose and continuous method performance can be monitored. This can be performed by using control charts or tracking system suitability data, method related investigations, and so forth. CMM allows the analyst to proactively identify and address any out-of-trend performance.

Advantages and Recommendations. AQbD is an approach that moves away from reactive troubleshooting to proactive failure reduction. The type and extent of the risk assessment depends on the stage of the project in the development timeline. AQbD success rate depends on right approach, planning, tools usage, and performance of work in a suitable time. Applying the appropriate risk assessment tools at the right time could lead to prevention of method failures and better understanding on the design space and control strategy [31–43].

9. Conclusion

Analytical Quality by Design (AQbD) plays a key role in the pharmaceutical industry for ensuring the product quality. The outcome of AQbD is the understanding from product development to commercial production. Scientist can easily identify the risk initially so that quality can be increased. AQbD tools are ATP, CQA, Method Optimization and Development with DoE, MODR, and Control Strategy with Risk Assessment, Method validation and Continuous Method Monitoring (CMM), and continuous improvement. AQbD requires the right ATP and Risk Assessment and usage of right tools and performing the appropriate quantity of work within proper timelines.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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