



## Pharmaceutical QbD: Concepts for Drug Product Development

Shalini Khatri<sup>1\*</sup>, Seema Saini<sup>2</sup>, Kuldeep gangawat<sup>3</sup>, S. Gurubalaji<sup>4</sup>

1. Masters in Pharmacy (Pharmaceutics), Rayat and Bahra Institute of Pharmacy, Rail Majra, SBS Nagar, Punjab, India.
2. Assistant Professor, Department of Pharmaceutics, Rayat and Bahra Institute of Pharmacy, Rail Majra, SBS Nagar, Punjab, India.
3. Sr. Research Executive, Formulation and Development Department, Nectar Life Sciences Limited, Saidpura, Punjab, India.
4. Sr. Scientist, Formulation and Development Department, Nectar Life Sciences Limited, Saidpura, Punjab, India.

\*Corresponding author's E-mail: [shalinikhatri12@gmail.com](mailto:shalinikhatri12@gmail.com)

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### ABSTRACT

Quality by design is an essential part of the modern approach to pharmaceutical quality. Quality by Design (QbD) has become a new concept for development of quality pharmaceutical products, it is an essential part of the modern approach to pharmaceutical quality, and QbD is a best solution to build a quality in all Pharmaceutical products. It is important to recognize that quality cannot be tested into products that is quality should built in by design. According to ICH Q8 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". This paper discusses quality by design and presents a summary of the key terminology. Under the concept of QbD throughout designing and development of a product, it is essential to define desire product performance profile (TPP, TPQP), Target and identify CQA. This leads to recognize the impact of raw materials (CMA, CPP) on the COAs and identification and control sources of variability. QbD is an innovative idea which offers pharmaceutical manufacturer with increased self-regulated flexibility while maintaining tight quality standards and real time release of the drug product. It also gives comparison between product quality by end product testing and product quality by Quality by Design. The concepts of QbD presented in this paper align with the principles of ICH Q8, Q9 and Q10 guidelines.

**Keywords:** QbD, CMA, design space, TPQP, CQA.

### INTRODUCTION

Aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. The Food and Drug Administration (FDA) and pharmaceutical industry are talking about quality by design, and related terminologies that are used as part of this discussion.<sup>2-7</sup> Traditionally, the relationship of product attributes to product quality has not been well understood, and thus regulatory agencies has ensured quality via tight specifications based on observed properties of exhibit or clinical trial batches and constraining sponsors to use a fixed manufacturing process. Pharmaceutical quality refers to product free of contamination and reproducibly delivers the therapeutic benefit promised in the label to the consumer. The Quality of the pharmaceutical product can be evaluated by in vitro performance tests and also quality by design assures product in vitro and in vivo performance. Hence quality by design relates to Product Performance. Pharmaceutical quality as a product that is free of contamination and reproducibly delivers the therapeutic benefit promised in the label to the consumer<sup>2</sup>.

Quality by Design (QbD) is a systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound scientific knowledge and quality risk mitigation assessment<sup>8</sup>. It means designing and developing

formulations and manufacturing processes to ensure a predefined quality. Thus, QbD requires an understanding how formulation and process variables influence product quality. Relevant reference documents from the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Q8 Pharmaceutical Development, along with ICH Q9, Quality Risk Management, and ICH Q10: Pharmaceutical Quality Systems, indicate on an abstract level how quality by design acts to ensure drug product quality.<sup>8, 9, 10</sup> Over the past several years, pharmaceutical scientists have provided several more specific definitions of what are the elements of quality by design and a draft of an annex to ICH Q8 has been released.<sup>3, 5, 10</sup>

Quality by Design (QbD) has become a new concept for development of quality pharmaceutical products, it is an essential part of the modern approach to pharmaceutical quality, and QbD is a best solution to build a quality in all Pharmaceutical products. Quality by Design (QbD) is a concept first outlined by well-known quality expert Joseph M. Juran in various publications, most notably Juran on Quality by Design.<sup>11</sup> QbD is a holistic approach where product raw material specifications, manufacturing process flow and critical process parameters are included in order to ease the final approval and ongoing quality control of new drug.

The application of QbD principles to pharmaceutical development and manufacturing has gained a lot of interest in the literature recently. The article describes a



systematic and general scheme to implement QbD in the pharmaceutical industry and also illustrate key aspect of QbD process in the pharmaceuticals.

**Pharmaceutical Quality by testing**

In this system, product quality is ensured by drug substance manufacturing, drug substance manufacturing, raw materials testing, a fixed drug product manufacturing process flow, in-process material testing, and finished product testing. The quality of raw material including drug substance and excipients is monitored by quality

control testing. If they meet the manufacture’s proposed and FDA approved specifications or other standards such as USP for drug substance or excipients, they can be used for manufacturing of the finished pharmaceutical products (FPP). Because of uncertainty as to whether the drug substance specification alone is sufficient to ensure quality, the drug substance manufacturing process is also tightly controlled. Figure 1 shows a simplified quality control diagram under the current quality by testing (QbT).<sup>12</sup>



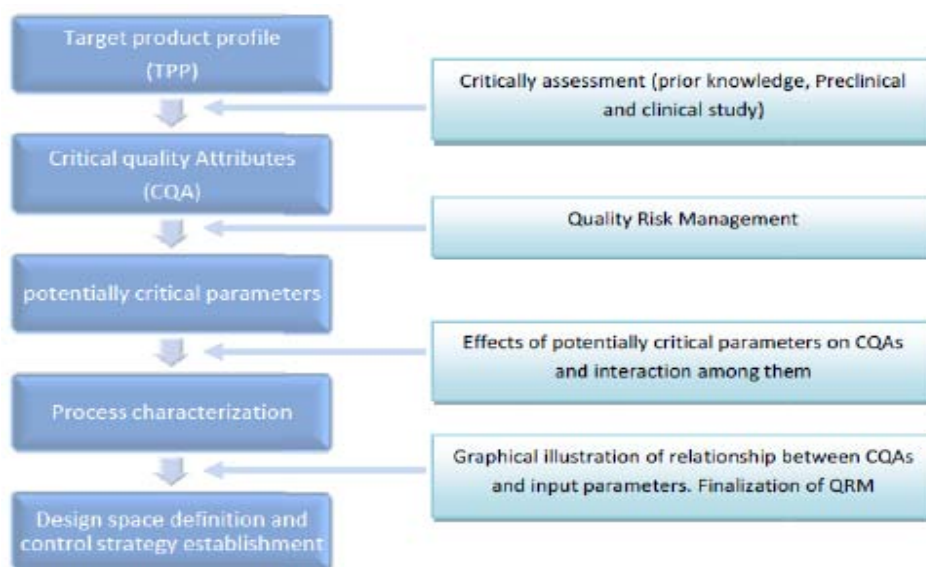
**Figure 1:** Flow Chart for Product Quality by End Product Testing

**Pharmaceutical Quality by Design**

We start with the assertion that Quality by Design (QbD) is a systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk mitigation assessment.<sup>8</sup>

It means designing and developing formulations and manufacturing processes to ensure a predefined quality. Thus, QbD requires an understanding how formulation and process variables influence product quality. ICH Q8 defines quality as the suitability, of either a drug substance or drug product for its intended use. Pharmaceutical QbD is a systematic, scientific, risk based, holistic and approach to pharmaceutical development that begins with predefined objectives and emphasizes product and processes understanding and process

control. It means designing and developing formulations and manufacturing processes to ensure predefined product quality objectives.<sup>1</sup> Knowledge management and quality risk management are two of the primary enablers of QbD. They are instrumental in achieving product realization, establishing and maintaining a state of control, and lastly facilitating continual improvement. Quality risk management is one of the tools that provide a proactive approach to identifying, scientifically evaluating, and controlling potential risks to quality. It also facilitates continual improvement in the product and process performance throughout the product life cycle. Knowledge management is a systematic approach to acquire, analyze, store, and disseminate information related to products, processes, and components. This also emphasizes on a transparency of information from development to commercial and vice versa.



**Figure 2:** Flow chart for Product Quality by design.

## Definition of QBD

The concept of “Quality by Design” (QbD) covers a better scientific understanding of critical process and product qualities, designing controls and tests based on the scientific limits of understanding during the development phase and using the knowledge obtained during the life-cycle of the product to work on a constant improvement environment. It is a systemic step wise approach to pharmaceutical development which design, analyze and control manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of new and in-process materials and processes, with the goal of ensuring final product quality, efficacy and safety. According to ICH Q8 QbD is defined as a systematic step wise 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.

## Elements of QbD<sup>13, 14</sup>

Pharmaceutical Development discusses the various elements of quality by design. These in combination with the enablers form the fundamental basis for the QbD approach to development.

QbD development process includes the following elements that accomplish the following steps as per figure 4.

1. To define the Target Product Profile (TPP) that describes the use, quality, efficacy and safety of the product.
2. To define a target product quality profile that will be used by formulators as a quantitative surrogate for aspects of clinical safety and efficacy during product development.
3. Determination of raw material Critical Quality Attributes (CQAs) of the final product that must be controlled to meet the target product quality profile (TPQP).
4. To establish the relationship between the drug and excipients attributes and the process parameters to the Critical Quality Attributes (CQA).
5. To define the Design Space.
6. Define the control strategy for the entire process that may include input raw material controls, process controls and monitors, design spaces around individual or multiple unit operations, and/or final product tests. The control strategy should encompass expected changes in scale and can be guided by a risk assessment.
7. Product lifecycle management & continual improvement of process to assure consistent quality.

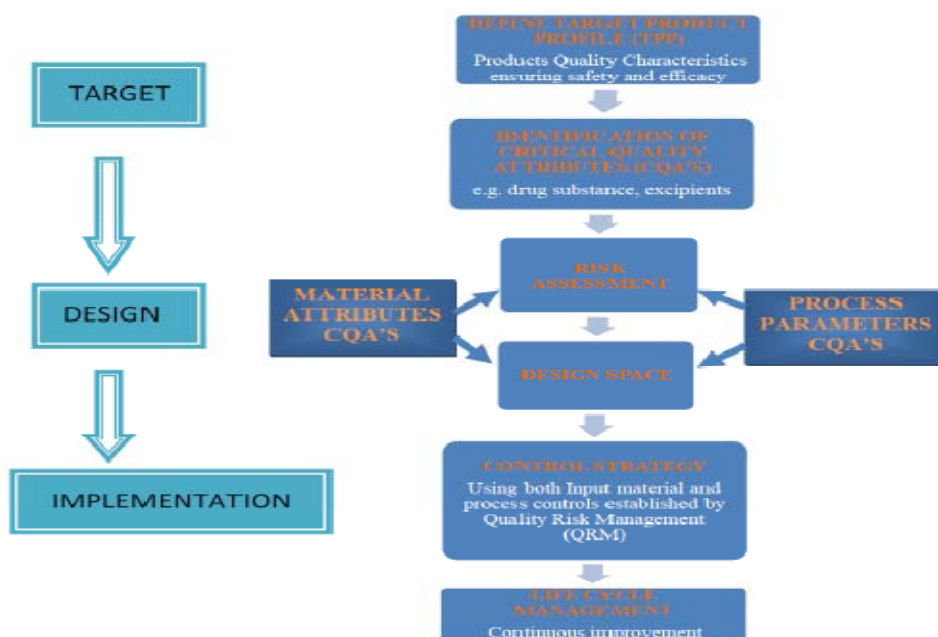


Figure 3: Key steps of Quality by Design.

## The Target Product Profile (TPP)

The target product profile (TPP) 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 are realized.<sup>15</sup> It is a tool for setting the strategic foundation for drug development planning with the end in mind. The target

product profile (TPP) is a summary of the drug development program described in the context of prescribing information goals.<sup>15, 16</sup> The target product profile describes the use, safety and efficacy of the product that initiates the development strategy. This target product quality profile will be used by formulators as a quantitative surrogate for aspects of clinical safety and efficacy during product development.<sup>17</sup> The TPP can

play a central role in the entire drug discovery and development process.

This includes dosage form and route of administration, dosage form strength(s), therapeutic form 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<sup>18</sup> The concept of TPP in this form and its application is novel in the QbD paradigm. The TPQP guides formulation scientists to establish formulation strategies and keep the formulation effort focused and efficient. TPQP is related to identification, assay, dosage form, purity, stability of the drug.<sup>16,18</sup> For example, a typical TPQP of an immediate release solid oral dosage form would include:<sup>19</sup>

- Tablet characteristics
- Identification
- Hardness
- Assay
- Content uniformity
- Dissolution
- Impurity
- Degradation profile
- Microbiology

#### Target product quality profile

The target product quality profile (TPQP) is a quantitative surrogate for aspects of clinical safety and efficacy that can be used to design and optimize a formulation and manufacturing process. International Society of Pharmaceutical Engineers (ISPE) Product Quality Lifecycle Implementation (PQLI) calls this the Pharmaceutical Target Product Profile.<sup>17</sup> It should include quantitative

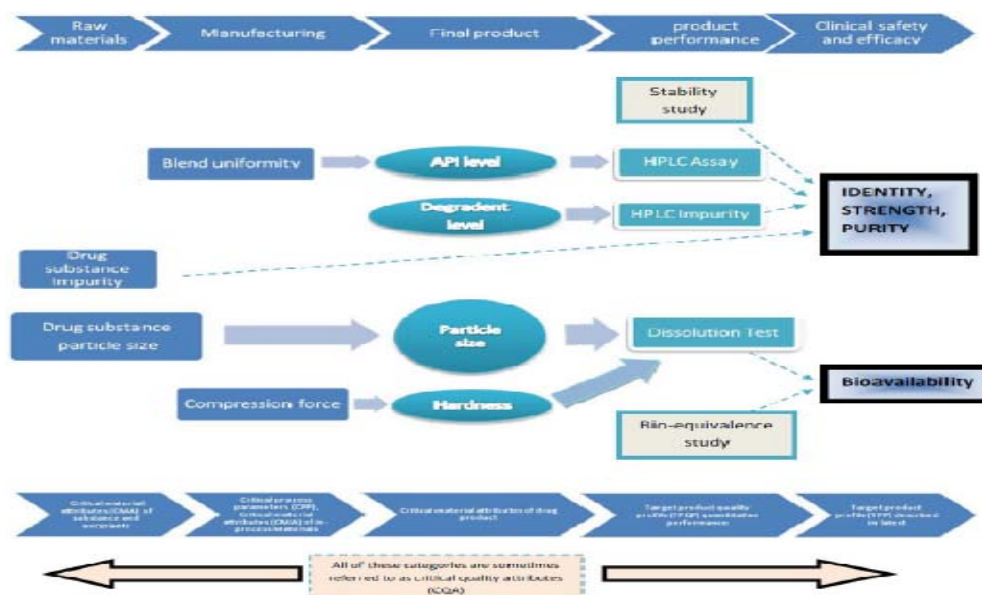
targets for impurities and stability, release profiles (dissolution) and other product specific performance requirements.

The TPQP of a generic drug can be readily determined from the reference listed drugs (RLD). Along with other available information from the scientific literature and possibly the pharmacopeia, the TPQP can be used to define product specifications to some extent even before the product is developed. Predefined, high quality product specifications make the product and process design and development more objective and efficient.

#### Critical Quality Attribute (CQA)

The ISPE PQLI defines critical quality attributes (CQAs) as physical, chemical or microbiological properties or characteristics that need to be controlled (directly or indirectly) to ensure product quality.<sup>5</sup> ICH Q8 (R1) defines CQAs as physical, chemical or microbiological properties or characteristics that should be within an appropriate working range or distribution to ensure the desired product quality. CQA has been used by some to describe elements of the TPQP (such as dissolution) while others have used CQA to describe mechanistic factors (such as particle size and hardness) that determine product performance.<sup>20,21</sup> Thus CQA is used to describe aspects of product performance and determinants of product performance.

It is necessary to identify the quality attributes that are critical, i.e. those defining purity, potency and surrogate for Bioavailability Criticality etc. It is based on the impact of quality attribute/ parameter on the safety, efficacy & quality (manufacturability) of the product. The level of criticality may differ for an API manufacturing process relative to a drug product manufacturing process. An illustration of QbD is explained in figure 4.



**Figure 4:** An illustration of how under QbD the identification of critical process parameters and critical material attributes is linked to the TPQP and finally to TPP that represents the clinical safety and efficacy.



## Identifying COAs

Once TPP has been identified, the next step is to identify the relevant COAs. Identification of COAs is done through risk assessment as per the ICH guidance Q9. Prior product knowledge, such as the laboratory skills, nonclinical and clinical knowledge with a specific product-quality attribute, is the key in making these risk assessments. Such knowledge may also include literature data from similar molecules and data from published literature. Taken together, this information provides a rationale for relating the COA to product safety and efficacy. The outcome of the risk assessment would be a list of COAs ranked in order of importance. Use of robust risk assessment methods for identification of COAs is novel to the QbD paradigm.

As a whole

- It is necessary to identify the quality attributes that are critical, i.e. those defining purity, potency and surrogate for bioavailability criticality etc. It is based on the impact of quality attributes/parameters on the safety, efficacy & quality (manufacturability) of the product.
- Establish a link between CPP & COAs: Identification of attribute or parameters that can be used as a surrogate for clinical safety & efficacy (important to patient).
- Manufacturability is also an attribute (important to business) that is critical to quality.
- The level of criticality differs from API manufacturing to drug product manufacturing process.
- As attribute or parameters boundaries approach edges of failure, the level of criticality increased with the risk.

## Critical Process Parameters

During process development, raw materials, process parameters and quality attributes are investigated. The purpose of these studies is to determine the raw material attributes, process parameters and quality attributes for each process and unit operations, and to establish any possible relationships among them. Critical quality attributes (COA) are physical, chemical or microbiological property or characteristic that must be controlled directly or indirectly to ensure the quality of the product. Critical process parameters (CPP) are process inputs that have a direct and significant influence on critical quality attributes when they are varied within regular operation range. Some have defined a critical process parameter (CPP) as any measurable input (input material attribute or operating parameter) or output (process state variable or output material attribute) of a process step that must be controlled to achieve the desired product quality and process consistency.

Process parameters can be understood as referring to the input operating parameters (mixing speed, flow rate) and

process state variables (temperature, pressure) of a process or unit operation. Under this definition, the state of a process depends on its CPPs and the CMAs of the input materials. Monitoring and controlling output material attributes can be a better control strategy than monitoring operating parameters especially for scale up. For example, a material attribute, such as particle size distribution, moisture contents, should have the same target value in the pilot and commercial processes. Operating parameters such as machine operating speed, equipment occupancy would be expected to change as the process scale changes.

For a given unit operation, there are four categories of parameters and attributes:

- Input material attributes
- Output material attributes
- Input operating parameters
- Output process state conditions

## Unclassified Process Parameter

There are many material attributes and process parameters that are important and even essential to product quality. All process parameters based on criticality is categorized as below. Thus three categories for attributes or parameters are proposed:

- Unclassified process parameter
- Critical process parameter
- non-critical process parameter

The criticality of an unclassified parameter is undetermined or unknown. These UPP may later be classified as critical or non-critical.

## Critical process parameter

A parameter is critical when a realistic change in that parameter can cause the product to fail to meet the TPQP. Thus, whether a parameter is critical or not depends on how large of a change one is willing to consider. A simple example is that an impeller speed of zero will always fail. Table 1 summarizes the proposed classification of process parameters.

## Design Space

Design space is defined as multidimensional combination of and interaction of input variables and process parameters that have been demonstrated to provide Quality Assurance. In the presence of interacting critical process parameters a design space is one approach to ensure product quality. The current definition of design space is "The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality." A design space may be constructed for all unit operations, or for the specific unit operations.



**Table 1:** Classification of Process Parameters

Parameter type	Definition	Sensitivity
<b>Non-critical process parameter (non-CPP)</b>	Not critical	No failure in target product quality profile (TPQP) observed or predicted in the potential operating space (POS), and No interaction with other parameters in the proven acceptable range (PAR).
<b>Unclassified process parameter (UPP)</b>	Critically unknown	Not established The default in the absence of pharmaceutical development.
<b>Critical process parameter (CPP)</b>	Critical (control needed to ensure quality)	Failure in target product quality profile (TPQP) observed or predicted in the potential operation space (POS), or Interactions with other parameters in the proven acceptable range (PAR)

**Critical concept behind design space:**<sup>22, 23, 24</sup>

- Multidimensional combination with interactions  
Multidimensional interactions put variables (e.g. raw material attributes) and process parameters.
- Demonstrated to provide assurance of quality of drug substance or drug product manufacturers.
- Defined by applicant and reviewed by regulator defined regulator.
- Once design space is approved, regulatory post approval change requirements will be simplified approval inside vs. outside design space inside space.
- Regulatory flexibility to operate within the design space of regulatory requirements.

**Development of design space: science based product and process design in development:**

- Enhance process understanding to support science based approach.
- Integration of drug substance and drug product process development at the interface.

**Utilization of design space: effective process control and quality system:**

- Use of extensive monitoring during development to enhance process understanding.
- Use science based control during manufacturing.

**Quality Risk Assessment**<sup>25</sup>

key objective of risk assessment in pharmaceutical development is to identify which material attributes and process parameters affect the drug product COAs, that is, to understand and predict sources of variability in the manufacturing process so that an appropriate control strategy can be implemented to ensure that the COAs are within the desired requirements During the initial phases of development, prior knowledge serves as the primary basis for the designation as there is not sufficient process/product understanding on the product under

development. Therefore, the risks identified at the initial phases are perceived risks and as further process/product understanding is gained, the actual risks become clearer and a control strategy can be better defined. The risk assessment tools used in earlier phases of development therefore tend to be more qualitative and serve as a means to prioritize the experimentation.

**Control Strategy**

Control strategy is defined as “a planned control operations, derived from current product and process understanding that assures process performance and product quality”.<sup>26</sup> The control strategy in the QbD is established via risk assessment that takes into account the criticality of the CQA and process capability. The control strategy can include the following elements: procedural controls process in process quality controls, lot release testing, process monitoring, physical characterization, comparability testing and ageing studies. It is worth noting that the use of risk assessment in creating the control strategy is unique to the QbD approach.<sup>1</sup>

A control strategy may include input material controls, process parameters, process operations and monitoring, design spaces around individual or multiple unit operations, and or final product specifications used to ensure consistent quality. A control strategy is uses to ensure consistent quality as they scale up their process from the exhibit batch presented in the ANDA to commercial production. Every process has a control strategy right now. The finished drug products are tested for quality by assessing if they meet specifications.

**Life Cycle Management**

A monitoring program for verifying the validity of process models should be established and be based on a risk analysis of the model itself and includes possible ways to verify the model by another means. Continuous improvement is an essential element in a modern quality system that aims at improving efficiency by optimizing a process and eliminating wasted efforts in production.



## CONCLUSION

Quality by design is an essential part of the modern reliable concept and is an innovative approach towards the pharmaceutical quality. This session intensifies the benefits of QbD as, establishment of TPP that elaborates the target for QbD in quantitative terms, identification and establishment of mechanistic link between critical material attributes and critical process parameters and determination of control strategy for incremental implementation of QbD elements in corresponding process within design space. Moreover paper also clarifies the use of QbD to determine specification for raw material, develop control strategies to mitigate risks and to reduce quality control testing. Principal of QbD facilitate development of quality products and their assessment throughout their lifecycle, and ultimately, result in greater patient compliance.

In such a way, this modern paradigm could be stands for essential benefits that lead to development of a quality pharmaceutical product with the continual improvement throughout the product lifecycle. The conclusion of QbD is focuses on building quality in the product and manufacturing process, as well as continuous process improvement, reduction of variability.

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