Compliance Considerations—FDA 2008 Process Validation Draft Guidance

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“Global Regulatory Viewpoint” addresses various regulatory and compliance topics including newly-published regulations from a global perspective. The content in this column is intended to be useful to those who deal with pharmaceutical development, development of CMC dossier sections, and guidances for manufacturing, validation, and CGMPs. The objective of this column: Useful information.

Reader comments, questions, and suggestions are requested to help us fulfill our objective for this column. Suggestions for future discussion topics are needed. Readers are invited to submit manuscripts for publication in this column. Please contact column coordinator Richard Poska at richard.poska@abbott.com or journal coordinating editor Susan Haigney at shaigney@advanstar.com.

KEY POINTS

The following key points are discussed in this article:

• The US Food and Drug Administration issued the draft guidance for industry Process Validation: General Principles and Practices, Draft Guidance in November 2008
• The guidance applies to manufacturing of human and animal drug products, including biological and biotech products, active pharmaceutical ingredients (API), and the drug component of medical device combination products
• The draft guidance aligns process validation with International Conference on Harmonisation (ICH) Q8, ICH Q9, and ICH Q10
• Quality and compliance personnel should be aware of this document because they often approve validation protocols and other validation documentation
• A new definition of process validation has been adopted by FDA
• The guidance proposes a lifecycle approach to process validation comprising three stages: Process design, process qualification, and continued process verification
• The process design stage defines the commercial manufacturing process, including process understanding and process control
• The process qualification stage confirms the work of the process design stage by demonstrating that the proposed manufacturing process is capable of reproducible commercial manufacture. Qualification includes
facility design and qualification of utilities and equipment and performance qualification (PQ).
• The continued process verification stage comprises activities to assure that the validated state of the process is maintained throughout routine commercial manufacturing.
• The guidance also addresses documentation and analytical methods.
• The new draft guidance reiterates principles stated in other guidances during the past 20 years, and attempts to integrate activities heretofore considered as separate and distinct. The recommendations of the new draft guidance are generally not new.
• Implementing the new guidance will require organizations to embrace the lifecycle approach to process validation, including enhanced organizational communication, collaboration, and documentation.
• Other areas for implementation include making sure performance standards throughout the product lifecycle are adequate, including emphasis on identification of potential input variation and routine use of statistical methods.
• Specific areas discussed in the guidance that warrant the attention of compliance personnel are described.

INTRODUCTION
The US Food and Drug Administration issued the draft guidance for industry Process Validation: General Principles and Practices, Draft Guidance in November 2008 (1). After final guidance approval, this document will replace the 1987 FDA process validation guidance (2).

Although the draft process validation guidance was not technically official at the time this article was written, it represents FDA’s latest thinking. This article addresses new or noteworthy elements in the draft guidance with specific emphasis on compliance. This document is especially relevant to quality and compliance personnel because validation is often part of the site quality organization, and the quality unit often approves validation protocols and other documentation.

The following topics are addressed in this article:
• Guidance overview
• Specific stage activities and other guidance recommendations
• Are these new requirements?
• Implications for compliance.

GUIDANCE OVERVIEW
The draft FDA process validation guidance applies to manufacturing of human and animal drug products, including biological and biotech products, active pharmaceutical ingredients (API), and the drug component of medical device combination products. The guidance aligns process validation with the global guidances of International Conference on Harmonisation (ICH) Q8, ICH Q9, and ICH Q10 (3,4,5) and embraces the product lifecycle concept. This approach links product and process development, performance qualification of the commercial manufacturing process, and ongoing maintenance of the process during routine commercial production. The guidance emphasizes science-based manufacturing, innovation, a thorough understanding of the process and control strategy, and continuous process improvement.

The 2008 draft guidance builds upon the 1987 guidance by adding elements of risk analysis, new technology, and quality systems. It is consistent with basic quality principles that a drug should be fit for its intended use as supported by the following basic tenets:
• Quality, safety, and efficacy are designed or built into the product
• Quality cannot be adequately assured merely by in-process and finished-product inspection or testing
• Each step of a manufacturing process is controlled to assure that the finished product meets all design characteristics and quality attributes including specifications.

A new definition of process validation is provided in the guidance as follows: “Process validation is defined as the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products” (1).
A lifecycle approach to process validation is described in the draft guidance that encompasses the following three specific stages:

- **Stage 1—Process Design:** The commercial process is defined during this stage based on knowledge gained through development and scale-up activities.
- **Stage 2—Process Qualification:** During this stage, the process design is confirmed as being capable of reproducible commercial manufacturing.
- **Stage 3—Continued Process Verification:** Ongoing assurance is gained during routine production that the process remains in a state of control (1).

A key section of the draft guidance clearly lays the foundation for what may be the essence of successful pharmaceutical manufacturing—understanding and control of potential sources of unexpected variation in manufacturing. Manufacturers should do the following:

- Understand and control the sources of variation
- Detect the presence and degree of variation that is abnormal for the system
- Understand the impact of variation on the process and ultimately on product attributes
- Control the variation in a manner commensurate with the risk it represents to the process and product.

### SPECIFIC STAGE ACTIVITIES

The key message of the draft guidance is that process validation should be an ongoing and coordinated effort throughout the organization. Process validation begins during the design and development of the product, API, etc., and continues throughout the entire product lifecycle. The draft guidance discusses recommendations and specific expectations for validation programs and for the respective stages of the lifecycle. The collaboration of relevant organizational groups including manufacturing, quality assurance, formulation, engineering, analytical, statistics, and other groups is recommended. The availability of expertise and relevant information from these groups with appropriate analysis will be useful to maintain continued successful manufacturing throughout the product lifecycle.

### Process Design

The process design stage is the initial stage of the product lifecycle. Work in this stage defines the commercial manufacturing process. It focuses on two main objectives: Process understanding and process control strategy. The main source of process understanding information lies in the product development effort which, in addition to original experimentation, can rely on previous knowledge. Traditionally, this information was warehoused in the research and development (R&D) area by scientists. To facilitate referencing in future submissions, it is now a key part of the regulatory submission. The publishing of ICH M4 (6) mandated the inclusion of specific development information in global regulatory submissions. The process design stage provides the basis for the manufacturing process as manifest in master batch records and in-process controls. The information developed (e.g., identification and understanding of the relationship of the important formulation and process variables) during this stage supports manufacturing throughout the entire product lifecycle. The application of statistical experimental designs associated with the quality-by-design (QbD) initiative is helpful to determine relationships and multifactorial interactions, design space limits, etc. Experimental work should be focused on appropriate highest risk processes as identified by risk analysis.

Development of a process control strategy has its foundation in the identification of the critical quality attributes. It should also reflect the understanding of the effects of various formulation and process variables on the quality attributes by the inclusion of in-process controls where necessary. These measures should minimize the reliance on end-product specification testing. Identifying potential sources of variation is another key element of the process design stage. Without control of input variables, successful manufacturing will not be possible. Often there is little experience with input variation at this stage of the product lifecycle. However, the potential for variation from equipment, different material lots, different production operators performing manual processes, environmental variation, and measurement systems in the production facility should be evaluated. When applied with a thorough understanding of the formulation and process, the use of...
process analytical technology (PAT) enables processing adjustments and is helpful to minimize output variation (7).

**Process Qualification**
The second stage of the product lifecycle is the process qualification stage. This stage confirms the work of the process design stage and demonstrates that the proposed manufacturing process is capable of reproducible commercial manufacture. The process qualification phase describes facility design and qualification of utilities and equipment and performance qualification (PQ).

Before conformance lots can be manufactured, the facility, equipment, utilities, and associated control systems must be demonstrated to be functioning properly (i.e., they must be qualified). The information in this activity is fairly standard IQ/OQ/PQ information. Risk management should be used to prioritize efforts. The draft guidance lists specific expectations for qualification of utilities and equipment including the following:
- Studies or tests to use
- Criteria appropriate to assess outcomes
- Timing of qualification activities
- Responsibilities
- Procedures that document and approve the qualification
- Requirements for evaluation of changes
- Documentation including summaries with conclusions that address acceptance criteria
- Approval by the quality unit.

Specific details of the PQ are discussed in the draft guidance. These include the PQ approach, PQ protocol, and protocol execution and report. This stage describes what many organizations currently understand to be the entire concept and practice of validation. Risk management should be used to define the relationship between the process variables and quality product attributes to ensure appropriate acceptance criteria. The PQ should be successfully completed before product is released for commercial distribution. The draft guidance specifically recommends that statistical metrics be used to achieve adequate assurance of acceptable processes. The PQ should have a higher level of sampling, additional testing, and greater scrutiny of process performance.

Specifics recommended in the draft guidance for the PQ protocol include the following:
- Manufacturing conditions including operating parameters, processing limits, and raw material inputs
- Data to be collected and how evaluated
- Tests to be performed and acceptance criteria
- Sampling plan including sampling points, number of samples, and frequency of sampling
- Number of samples should be adequate to provide statistical confidence of quality within and between batches.
- Confidence level can be based on risk analysis
- Sampling should be more extensive than in routine production
- Acceptance criteria should specify statistical methods
- Provision for addressing deviations and handing non-conforming data
- Data should not be excluded from the PQ without a documented science-based justification
- Approval by the quality unit.

Specifics recommended for protocol execution and report in the draft guidance include the following:
- Protocol execution should not begin until protocol has been reviewed and approved
- Commercial manufacturing process and routine procedures must be followed under normal conditions and by normal manufacturing personnel
- Final report should discuss all aspects of the protocol, summarize and analyze all data, evaluate unexpected observations and non-conformances, and describe corrective actions or changes to existing procedures and controls
- State a clear conclusion that the process met expectations. If it did not, discuss future actions planned to complete the PQ
- Approval by the quality unit.

**Continued Process Verification**
Continued process verification comprises activities to assure that the validated state of the process is
maintained throughout routine commercial manufacturing. Current good manufacturing practice (CGMP) currently requires a system to collect and assess product data, and specifically to detect process shift or drift. The draft guidance states that data collected should include relevant process trends and quality of incoming materials or components, in-process material, and finished products. Data should be statistically trended and reviewed by personnel trained in statistical methods to confirm that critical quality attributes are well controlled. Procedures should describe how trending and calculations are done. These data can help to identify process and product variability and cause improvements to be initiated. The use of statistical methods to determine variation, characterize it, and identify root causes is recommended. Also recommended is the scrutiny of intra-batch and inter-batch variation.

The draft guidance recommends continued monitoring and/or sampling at PQ levels until sufficient data are available to generate significant variability estimates. Thereafter, sampling can be adjusted to a statistically appropriate level. Other areas for monitoring identified in the draft guidance include the following:

- Product complaints
- Out-of-specification (OOS) findings
- Process deviation reports
- Process yield variations
- Batch records
- Incoming raw material records
- Adverse event reports.

Production line operator and quality staff feedback on process performance should be solicited. Operator errors should be tracked to measure the quality of training programs; to identify operator performance issues; and to look for potential batch record, procedural, and/or process improvements to help reduce operator errors. The quality unit should periodically meet with production staff to evaluate data, discuss trends, and coordinate corrections or follow-up actions by production. Production operators are often good sources of information and are usually overlooked. Other elements of the process should also be evaluated in a similar fashion.

Maintenance of the facility, utilities, and equipment is also mentioned in the draft guidance as important to process control. Qualification status must be maintained by routine monitoring, maintenance, and calibration programs.

**Other Guidance Recommendations**

Two other areas briefly discussed in the draft guidance include documentation and analytical methods. Documentation during the entire product lifecycle is essential. A system that enables the ability to retrieve documentation for use throughout the product lifecycle is equally important. Design and development information generated during product development should be used as needed throughout commercial manufacturing so that science underlies process decisions. Process qualification documentation and process monitoring documentation are mandated by CGMP and are generally easily accessible. FDA recommends use of process flow diagrams throughout the development and commercial process to facilitate comparison and evaluations for comparability.

The draft guidance discusses the importance of accurate and precise analytical results throughout the product lifecycle. Validated analytical methods are not required during product development activities. However, scientifically sound methods must be used, and analytical equipment must be functioning properly. This is especially important when attempting to correlate development data and commercial product data.

**ARE THESE NEW REQUIREMENTS?**

Although the draft process validation guidance was issued in November 2008, the content of the guidance was generally well known prior to actual issue. The comprehensive and integrated lifecycle approach to process validation has been clearly discussed in recent regulatory presentations, and the various specific topics associated with the approach have also been published for many years. Essentially everything stated in the 2008 draft guidance should have been expected.

FDA representatives have clearly presented the lifecycle approach for several years (8,9,10). These presentations have included comments on factors indicating the need for the lifecycle approach. The
lifecycle approach overcomes the “checklist” mentality to process validation in which process validation is considered to be a singular event. Encouraging comprehensive process understanding improves technical analysis if manufacturing problems occur. Successfully manufacturing three validation lots does not provide good assurance that future manufacturing will be reliable. The 2004 revision of the FDA Compliance Policy Guide (11) clearly states that manufacturers should have enough data and knowledge about the commercial production process to support post-approval product distribution. Also, the manufacturer should identify and control all critical sources of variability prior to conformance batches and commercial manufacturing.

Some of the key concepts in the 2008 draft process validation guidance were actually mentioned in the 1987 guidance. For example, the 1987 guidance mentions “...adequate product and process design...” “...quality, safety, and effectiveness must be designed and built into the product...”, and “During the research and development (R&D) phase, the desired product should be carefully defined in terms of its characteristics, such as physical, chemical, electrical, and performance characteristics.” In addition to discussing actual validation protocols, the document mentions several post validation considerations: “...quality assurance system in place which requires revalidation whenever there are changes in packaging, formulation, equipment, or processes which could impact product effectiveness or product characteristics, and whenever there are changes in product characteristics.” “The quality assurance procedures should establish the circumstances under which revalidation is required.”

The various FDA guides to inspections (12,13,14), all issued during the 1990s, further the concepts of the 1987 guidance. They emphasize the development phase of the validated process. This includes documented experiments, data, results, control of the physical characteristics of the excipients, particle size testing of multi-source excipients, and determination of critical process parameters. Development data serves as the foundation for the manufacturing procedures, and variables should be identified in the development phase. Raw materials were identified as a source of lot-to-lot variation. The 1987 guidance also mentions post validation considerations such as evaluation of changes in packaging, formulation, equipment, or processes which could impact product effectiveness or product characteristics (i.e., the validated state must be maintained).

Consistency With Other Regulatory Guidances
The draft process validation guidance is consistent with ICH Q8, Q9, and Q10 documents. These documents provide current global thinking on various aspects of the product lifecycle from development through commercialization. They provide a comprehensive and integrated approach to product development and manufacturing to be conducted over the lifecycle of the product. ICH Q8 discusses information for regulatory submission in the ICH M4 Common Technical Document format. ICH Q8 describes a comprehensive understanding of the product and manufacturing process that is the basis for future commercial manufacturing. ICH Q9 provides a systematic approach to quality risk management through various risk assessment tools. ICH Q10 complements Q8 and Q9, and discusses the application of the various quality system elements during the product lifecycle. Elements of the quality system include process performance monitoring, corrective action and preventive action (CAPA), change control, and management review. These quality system elements are applied throughout the various phases of the product lifecycle.

The 2000 ICH Q7 (15) Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients discusses activities conducted prior to and post validation. For example, ICH Q7 states that critical parameters and attributes should be identified during development, and these critical process parameters should be controlled and monitored. Non-critical parameters should not be included in validation. Regarding post validation, there should be periodic review of validated systems.

Improved process understanding as described in the process design stage of the lifecycle approach to process validation is completely consistent with the QbD initiative and associated initiatives such as PQLI (16) and Conformia (17). The ANVISA Good Manufacturing Practices for Medications Technical Regulations: Basic
Principles (18), which was issued in 2009 for comment, is also consistent with the FDA draft process validation guidance.

IMPLICATIONS FOR COMPLIANCE
While the draft process validation guidance was not technically official at the time this article was written, significant changes in this document are not expected. As described previously, the content of the draft guidance does really not suggest any new requirements by FDA—it is primarily an update based on previous requirements from earlier FDA documents, ICH quality guidance documents, and recent FDA presentations.

One reason FDA issued the draft guidance was that current validation practice has evolved into a “checklist” activity in which process validation was a singular event. In contrast, the new draft guidance emphasizes a lifecycle approach to process validation with emphasis on technical science throughout. Compliance professionals should be mindful of this change in focus and be sure that their organizations have a corresponding mindset. Also, the draft guidance discusses several new areas of emphasis. Compliance professionals should likewise focus on these new areas and encourage corresponding organizational response.

We see the following two general concepts to be discussed regarding compliance with the draft guidance:

- **Lifecycle approach to process validation.** Acceptance of this concept will require enhanced organizational collaboration, communication, and documentation.
- **Performance standards throughout the product lifecycle.** This includes specifics mentioned in the guidance as well as increased emphasis on identification of potential input variation and use of statistical methods.

**Lifecycle Approach To Process Validation**
In contrast to the current prevalent business model of validation as a singular event, organizations must embrace the lifecycle approach to process validation. This will require a comprehensive view of validation rather than focus on the performance of the usual three conformance lots. Many firms organize their operations in distinct silos, for example, R&D, manufacturing, validation, and quality. The silos create barriers to communication and cooperation. The R&D organization develops the product; once development and approval is completed, the product is transferred to manufacturing. Manufacturing then makes the process ready for validation and routine commercial manufacturing. The validation function coordinates process validation. After the conformance lots are successfully completed, the validation effort is finished. Manufacturing then continues routine commercial production with oversight by the quality unit. There is usually minimal ongoing interaction between R&D, validation, manufacturing, and quality. It is clear that there will be an increased reliance on how effective the process understanding gained through development is shared across disciplines within each company.

In the lifecycle approach to process validation, there are ongoing interactions between all groups. The technical development work that is the basis for the formulation and process should be continually used to support process changes and as a benchmark in the ongoing evaluation of process performance. A successful lifecycle approach to process validation requires ongoing interaction and communication between all affected groups. With this in mind, compliance personnel should do the following:

- Ensure the availability of technical documentation supporting a thorough understanding of the product formulation and process. This includes justification for any changes that are needed during the entire product lifecycle.
- Ensure that the critical quality attributes and critical process parameters are identified, and that the appropriate in-process controls and final product testing that comprise the total control strategy are identified.
- Consider the manufacture of the conformance lots as a “snapshot in time,” and not the final word or action on validation. The validated state must then be maintained through process monitoring, technical data evaluation, and change control. Maintaining the product and process validated state is key.
- Ensure that manufacturing “fixes” or “tweaks” are evaluated by technical people and made...
only when supported by robust data sets or control charts.

- Require involvement of technical people in process improvements and be sure that they provide technical justification for these improvements
- Foster an ongoing collaboration and communication among all relevant organizational areas. Organizational silos must be transformed into interactive units.

**Collaboration, communication, and documentation.** The lifecycle approach to process validation requires enhanced organizational communication, collaboration, and documentation. Compliance personnel should do the following:

- Require scientific and technical reports as the basis for the formulation and process
- Ensure reports are accessible as needed throughout the entire product lifecycle
- Ensure reports are easily retrievable for technical consultation and reference in audits.

**Performance Standards Throughout The Product Lifecycle**

The draft guidance states specific expectations for the various stages in the lifecycle approach. Compliance personnel should ensure compliance with these specific expectations. The following are examples:

- In process qualification, the PQ protocols should specify the data to be collected and how evaluated; tests to be performed and acceptance criteria; and sampling plan including sampling points, number of samples, and frequency of sampling. These requirements should be clearly stated and justified in the protocols.
- In conformance lots, the commercial manufacturing process and routine procedures must be the same as those to be followed under routine manufacturing conditions
- In continued process verification, product complaints, OOS findings, deviations, yields, and adverse event reports should be regularly monitored. There should be regular review of production line operator and quality staff feedback on process performance. Operator errors should be tracked. The quality unit should periodically meet with production staff to evaluate data, discuss trends, and coordinate corrections.
- All equipment, utilities, facilities, and analytical methods must be validated
- All testing and generated data must be consistent with the product and process control strategy.

**Identification of potential input variation.** The identification and control of potential input variation was specifically emphasized in the draft process validation guidance. This includes identification of the variation each unit operation is likely to encounter, as well as the range of expected variability. Process inputs with important sources of variation may include materials, equipment, processes, measurement systems, manufacturing staff, and the manufacturing environment. Compliance personnel should assess the following and initiate corrective action as appropriate:

- Are processes robust and yield acceptable product despite reasonable variation in process inputs?
- Are materials including active drug and inactive excipients adequately controlled including defined specifications for key physical properties? If the active drug is quantitatively a minor part of the formulation, it may be more important to control the particle size of major inactive excipients to assure a repeatable process.
- Are personnel who influence process parameters and variables and operate equipment adequately trained? Ongoing monitoring of operator performance is critical to minimize human factor effects on processes.
- Strategies to control raw material variation, equipment performance variation, process testing requirements, personnel variables, and other sources of variation should be available as part of development or the technical support effort.
- Compliance personnel should question process steps with conflicting outputs (e.g., increasing drying conditions to minimize API degradation may cause particle size reduction that negatively impacts processing). Process steps may have positive and negative ramifications.
Statistical methods. The use of statistical methods is specifically mentioned in several areas of the draft guidance. Statistical methods, including screening studies and design of experiments (DOE), are commonly used in product development. The draft guidance specifically identifies statistical applications in the process qualification stage and the continued process verification stage. Compliance personnel should consider the following and initiate corrective action as appropriate:

- The number of samples should be adequate to provide statistical confidence of quality within and between batches
- Acceptance criteria should specify statistical methods
- Monitoring data collected throughout the product lifecycle should be assessed and trended to detect process drift. Data collected should include relevant process trends and quality of incoming materials or components, in-process material, and finished products.
- Data should be statistically trended and reviewed by personnel trained in statistical analysis to confirm that critical quality attributes are well controlled
- There should be procedures to describe how trending and calculations are done. These data can help to identify process and product variability and cause improvements to be initiated.
- Statistical methods to determine variation, characterize it, and identify root causes are recommended
- The use of industry accepted methods such as control charting provide the basic tools needed to interpret data to make them meaningful over extended periods of time. The use of statistical indices (e.g., cPk) can also be used to predict the robustness of the process as measured by each proposed control.

CONCLUSIONS

Although FDA issued the draft process validation guidance in 2008, the information therein is not really new. Compliance professionals who are aware of ICH guidances and FDA chemistry, manufacturing, controls (CMC) initiatives including the QbD effort should not be surprised by the content of the draft guidance. Also, they should be gratified to see FDA embracing these principles in terms of their application to process validation. These requirements have long been signaled. Most of these requirements have also been previously published in documents over the past 20 years. The new guidance recommends a coordinated and comprehensive effort in validation as opposed to addressing validation as a distinct and singular event.

The primary challenge for industry to implement the recommendations of the draft guidance is to develop coordinated systems in their organizations. These systems should support a multi-disciplinary approach to product development to develop an understanding that is supportive to robust product manufacturing through its lifecycle. The information and activities recommended in the guidance are generally already in place; however, the appropriate “warehousing” of this information is not always as obvious. What will be needed is increased communication between organizational groups, greater availability of technical reports, coordinated decisions involving appropriate organization experts, and so on. Another challenge faced is how best to present the increasingly technical information within the organization and to the regulatory authorities. Organizations must also be sure they are compliant with standards as stated for the three lifecycle stages of validation. Special emphasis should be placed on identification and control or input variation and on the application of statistics in all phases of the product lifecycle.

The draft guidance and its clarified expectations should help organizations focus on key areas. There is definite consistency in the messages of US and international guidelines. The draft guidance provides general areas of focus for organizations as well as very specific directives with these areas. Compliance personnel should evaluate their organizations regarding organizational collaboration, communication, and documentation relative to the lifecycle approach to process validation. Compliance personnel should also evaluate the specific performance standards stated in the guidance throughout the product lifecycle. This includes an increased emphasis on identification of potential input variation and use of statistical methods.

ACKNOWLEDGMENT

Helpful discussions with Richard Poska and J. Ambrose Van Wert are appreciated.
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ARTICLE ACRONYM LISTING
API Active Pharmaceutical Ingredient
CAPA Corrective Action and Preventive Action
CGMP Current Good Manufacturing Practice
CMC Chemistry, Manufacturing, Controls
DOE Design of Experiments
FDA US Food and Drug Administration
ICH International Conference on Harmonisation
IQ Installation Qualification
OOS Out-of-Specification
OQ Operational Qualification
PAT Process Analytical Technology
PQ Performance Qualification
QbD Quality by Design
R&D Research and Development

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