
formulation

CONTROL STRATEGY CONSIDERATIONS
DURING FORMULATION AND PROCESS
DEVELOPMENT

ROBERT J. TIMKO
RHOTAU PHARMA
SERVICES



Control strategy is a key element of drug product development. For tablets and capsules, it involves understanding the product and process development and the relationships among the materials, equipment, process, and facility attributes. While creating a design space may be optional, a control strategy is required regardless of whether you undertake a traditional or Quality-by-Design approach to development.

Tablets and capsules have long been the primary platforms for reliable delivery of safe, efficacious pharmaceutical products. Compressed tablets originated in England in the early 1840s, and the use of capsules can be traced back to the early 18th century. Given that history, one would expect that the scientists who develop these solid dosage forms and specify how to manufacture them would have a good understanding of the important quality attributes that are required to ensure a commercially viable product.

Yet the development paradigm is not always well documented. Listed below are some typical comments made by the FDA in the review of several recent New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs) regarding the manufacture of immediate- and extended-release solid dosage forms:

- How are the manufacturing steps (unit operations) related to drug product quality?
- How were the critical quality parameters identified, monitored, and/or controlled?
 - No details are provided for identifying, monitoring, and controlling the critical process parameters (CPPs) in the drug product. It is not clear how both the manufacturing process and CPPs were identified as no actual experimental data are provided.
 - Many of the process parameters in each unit operation are listed as “criticality undetermined” or “not critical”; please provide your risk assessment for all process parameters for each unit operation. Please provide the control strategy for this product based on product development information.
 - Please provide an updated flow chart and manufacturing description indicating each unit operation, in-process control points, and in-process tests to be conducted at each control point.
 - The table identifying the critical quality attributes (CQAs) from the quality target product profile (QTPP) identified drug product attributes as “not critical” because they do not affect safety and efficacy. However, these CQAs may have an impact on drug product quality attributes, such as assay. Please re-evaluate and provide an updated control strategy.

If you're a formulator developing a drug product, it is paramount that you know and understand how the product will be manufactured in a production setting. This is a key element of the formulation and process development paradigm and an essential building block of a high-quality product.

High quality requires good planning

It is a simplistic analogy, but think of formulation development in terms of developing the recipe for a cake. The result should mimic a packaged cake mix, which includes or lists all the ingredients required and provides complete yet simple instructions. By using these ingredients and following the directions, you create a cake that has the appearance, texture, and taste described in the product's literature. The cake mix represents a well-defined formulation, manufacturing process, and control strategy that enables a home baker to produce a delicious dessert.

Whether it is a cake, tablet, or capsule, the formulation development process is the same: Identify the ingredients and their essential properties and quantities. Likewise with process development: Specify the equipment, CPPs, and times. The result is a formulation and manufacturing process with a defined control strategy, which should give you a product that can be manufactured over and over again to its defined quality standard.

Quality by Design (QbD) for product development and manufacture is a concept that states that quality can be planned and that most quality problems relate to the way in which quality was planned. QbD principles have been used to advance product and process quality in many industries. In fact, almost all commercial products outside pharma use manufacturing techniques that ensure product quality by building it into the process used to manufacture the product. Very few products are release-tested to ensure that they meet their design specifications prior to commercial distribution. If done properly, this same concept should work with pharmaceutical products. Thus, in last decade or so the FDA has promulgated QbD as part of its 21st Century Initiative as a vehicle for transforming how drug products are developed and manufactured.

The FDA's 2004 “Guidance for Industry: PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance” introduced the concept of building quality into the preparation of drug products through the use of Process Analytical Technology (PAT). The goal was to replace end-product testing as a means of ensuring that a product met its specifications. The International Committee on Harmonization (ICH)—with the help of pharma and global health authorities—has also issued guidance documents, Q8 through Q11, that describe how QbD concepts apply to the lifecycle of a drug product. See Table 1.

In short, quality can be designed into tablet and capsule products if you follow well-defined development practices. It starts with gaining product and process understanding, followed by identifying, evaluating, and minimizing risk. To achieve the required safety, efficacy, manufacturability, and stability using QbD, follow these steps:

- Define the QTPP, which describes the design profile of the product and forms the basis for the development of the quality attributes that ensure clinical safety and efficacy. The QTPP also forms the basis for the control strategy.
- Review prior knowledge, including the scientific literature and any experience with similar dosage forms and/or with APIs that have similar properties.
- Evaluate the physicochemical properties of the API and how potential excipients could affect the dosage form.
- Conduct an assessment to identify, understand, and minimize the potential risks associated with the preparation that may affect manufacturability, safety, or efficacy.
- As needed, conduct studies to facilitate and understand the product's design and the manufacturing process.
- Develop a control strategy to ensure that the product will have the required quality attributes and be consistently produced. This control strategy will be derived from product and process understanding and should ensure that the process performs as designed and gives the specified product quality.

Select a control strategy approach

The control strategy plays an important role in ensuring that the QTPP is realized and the CQAs met. It is

TABLE 1**ICH quality guidances**

ICH Q8 (R2)—Pharmaceutical Development	Current Step 4 version, August 2009
ICH Q9—Quality Risk Management	Current Step 4 version, November 2005
ICH Q10—Pharmaceutical Quality System	Current Step 4 version, June 2008
ICH Q11—Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)	Current Step 4 version, May 2012
Pharmaceutical Quality Training Program for Q8/Q9/Q10	
Quality Implementation Working Group on Q8, Q9 and Q10: Questions & Answers (R4)	Current version, November 2010
ICH Quality Implementation Working Group Points to Consider (R2), ICH-Endorsed Guide for ICH Q8/Q9/Q10 Implementation	Current version, December 2011

not just a concept, nor is it optional. It is also not a specification. Each product requires an overall control strategy, and there may be more than one approach to creating it. For instance, you may want to develop a control strategy for each unit operation, which can include site-specific details.

Regardless whether you develop a control strategy using a traditional or QbD approach, the effort should begin during formulation and process development and continue through commercial manufacture. The identification and understanding of the links between the CQAs and the formulation and processing variables are key to formulation and process understanding and to risk analysis and mitigation.

A well-defined control strategy reduces risk but does not change the criticality of the attributes. The goal is to gain product and process understanding and to identify the sources of variability that can affect product quality. Once you understand these sources of variability and their impact on the downstream processes, in-process materials, and drug product quality, you can—if necessary—shift controls upstream and minimize the need for end-product testing. Only by identifying the potential for harm can you estimate the probability of its occurrence.

Which approach to developing a control strategy you select will depend on many factors, including, for example, analytical testing sensitivity, equipment limitations, and processing capabilities. Also, consider sharing your control strategy with regulatory affairs personnel so they can determine whether the risks have been adequately controlled to meet the expectations of health authorities.

Once the control strategy is adapted to and implemented at production scale at the manufacturing site, inspectors from the health authority may review it during inspections to ensure its adequacy and determine whether the site's quality system can support it.

Control strategy is generally initiated during the clinical trial phase and must be refined for use in commercial manufacture as you gain more information and knowledge. As part of scale-up and technical transfer, product attributes are assessed to determine their impact on product quality. This evaluation and refinement should be continuous to ensure a robust control strategy over the lifecycle of the drug product.

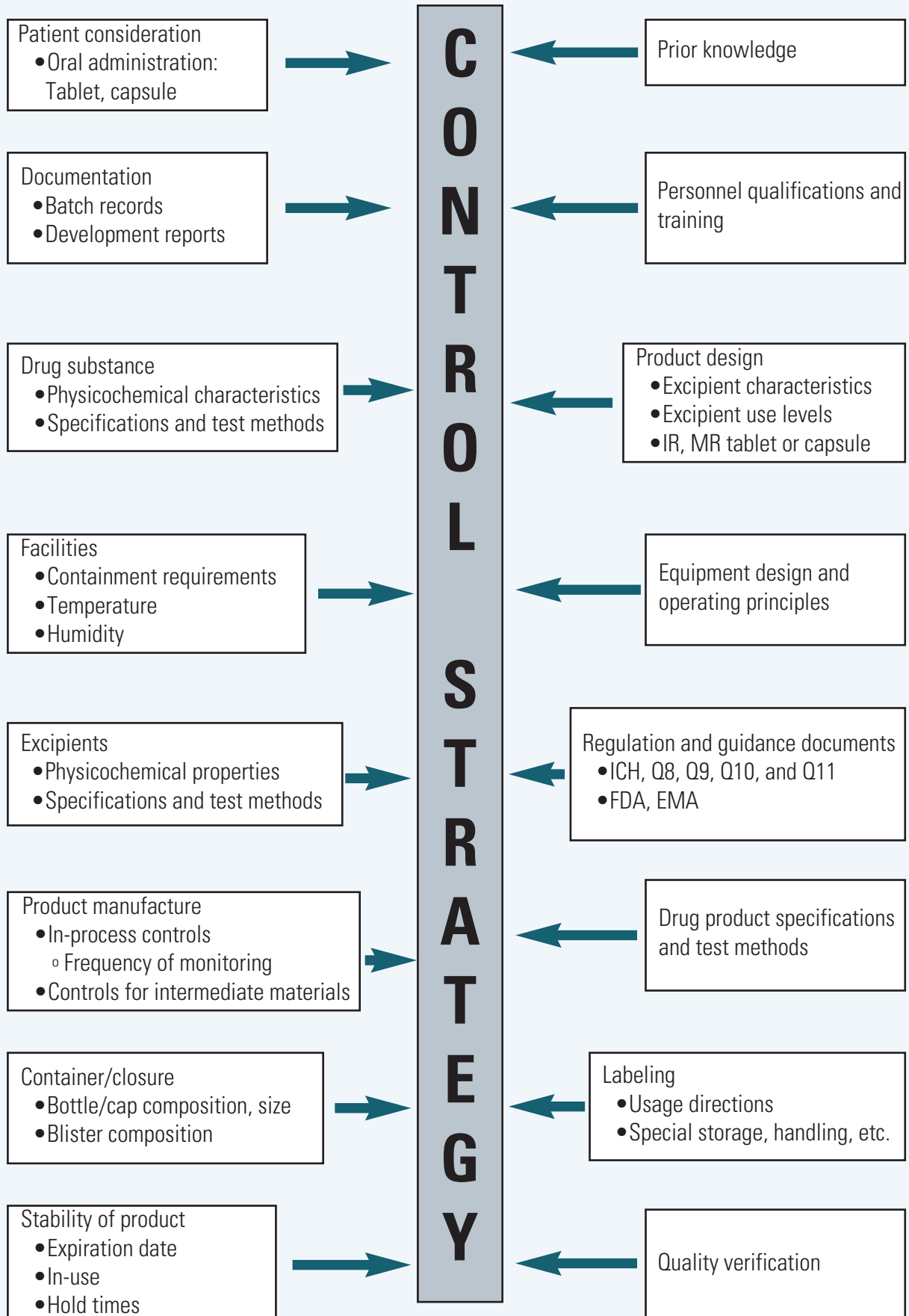
The control strategy for each drug product should contain an understanding of the chemical and physical characteristics of the API and excipients. It may also involve aspects that are specific to the manufacturing site, such as temperature, humidity, or containment requirements. Additionally, there may be specific equipment characteristics or operating parameters that are important to product quality. Other considerations may include what controls are needed to adjust the process and/or ensure the quality of intermediates, how to monitor those controls, and what in-process tests are required. Containers/closures and storage conditions may also warrant consideration.

A control strategy can be divided into more than one level. There is the operational level—tied to the manufacturing process—which would include, for example, processing parameters and material attributes. The quality assurance level would include overseeing the operational level and using risk assessment/risk analysis to determine whether a change in a material attribute or process parameter is within the design space or proven acceptable range. The strategic level relates to regulatory robustness, i.e., what is written in the documentation approved by the FDA. This defines what action may be required to implement changes to approved NDA or ANDA documents. Figure 1 summarizes considerations typical for most control strategies.

Don't confuse the control strategy with batch release. The control strategy is an element of batch release, but not the only element needed for making a batch-release decision. The elements of control strategy that contribute to final product quality may include, as discussed above, in-process controls and the controls for input materials such as APIs, excipients, intermediates, and containers/closures. The control strategy also encompasses the drug product, facilities, equipment operating conditions, frequency of monitoring, finished-product specifications, and analytical methods.

Clarity in documentation

The better you understand and apply QbD concepts when developing the documentation to be included in an NDA or ANDA, the less likely the FDA will require additional information during the review process or when you seek to make a post-approval change. Be sure your docu-

FIGURE 1**Typical control strategy considerations**

ments are written clearly, use easily understandable language, and meet the required format.

The documents should, for instance, define the formulation and process studies that were conducted and state what was learned from each experiment. Using this information, construct a risk evaluation of what may be critical or not critical in defining the unit operations. Provide a detailed flow chart and describe each unit operation. Discuss each processing step, its purpose, and how it affects overall product quality. Identify the critical material attributes of the API, excipients, and/ or intermediates and the CPPs. Determine how often these attributes and parameters require monitoring and control to ensure a consistently high-quality finished tablet or capsule based on the risk assessments you performed.

Explain your reasoning. Provide experimental data that justify your decisions and/or, if necessary, conduct additional studies to provide missing data. Never make any statement that implies that the criticality of a material or process attribute is undetermined or unknown, because that reveals that your development work is insufficient to understand the product, to assess its CQAs, or to propose a suitable control strategy. T&C

References

R. Mestel, "The Colorful History of Pills Can Fill Many a Tablet," *Los Angeles Times*, Mar 25, 2002.

"Guidance for Industry: PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance," U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM), Office of Regulatory Affairs (ORA), Pharmaceutical CGMPs, September 2004.

"Pharmaceutical cGMPs for the 21st Century: A Science and Risk Based Approach." FDA. Online. Accessed May 25, 2017.

M. Glodek et al., "Process Robustness—A PQRI White Paper," *Pharm Eng* 2008 26(26): 1-11.

R. Iser and A. Srinivasan, "FDA Perspectives: Common Deficiencies in Abbreviated New Drug Applications: Part 1: Drug Substance," *Pharm Tech* 2010 34:1.

J. Piriou, B. Elissondo, M. Hertschuh, and R. Ollivier, "Control Strategy as the Keystone of the Product Lifecycle, from Product/Process Understanding to Continuous Process Verification and Understanding," *Pharm Eng* 2012 2(1): 1-8.

J.F. Skaftason and T. Johannesson, "Tablets and Tablet Production—with Special Reference to Icelandic Conditions," *Laeknabladid* 2013 99(4): 197-202.

G.A. Van Buskirk et al, "Best Practices for the Development, Scale-up and Post-Approval Change Control of IR and MR Dosage Forms in the Current Quality-by-Design Paradigm," *AAPS PharmSciTech* 2014 15(3): 665-693.

LX Yu et al, "Understanding Pharmaceutical Quality by Design," *AAPS J* 2014 16(4): 771-783.

T. Mire-Stuis, B. Kuhn, and T. Monica, "Development of Integrated Control Strategies and PV Plans for US and European Filings," *CASSS CMC Strategy Forum Europe*, 2014.

S. Pope-Miksinski, "Regulatory Considerations in the Development and Communication of Control Strategy," *CMC Workshop, ONDP, FDA*, 13 April 2015.

S. Pope-Miksinski, "Integrated Quality Assessment: An Update on Team-Based and One Quality Voice," *DIA CMC Workshop, ONDP, FDA*, 14 April 2015.

R. Iser, "Life-Cycle Management—FDA Perspective," *Office and Process and Facilities, OPQ, FDA, DIA CMC Workshop, April 13-15 2015, Bethesda, MD*.

Risk Ranking and Filtering, PQRI, Risk Management Training Guides, Manufacturing Technology Committee—Risk Management Working Group, pp 1-8.

Robert J. Timko, RPh, PhD, is president of RhoTau Pharma Services, 920 Sassafras Circle, West Chester, PA 19382. Tel. 484 437 2654. Website: www.RhoTauPharma.com. His consulting work focuses on helping companies optimize their development and supply chain footprints leading to successful product commercialization. He has more than 40 years of industry experience in developing a variety of dosage forms from both pharmaceutical development and regulatory affairs perspectives.

Further reading

To find more information about the topics discussed here, search for articles listed under "Excipients," "Formulation," and "Quality by Design" in *Tablets & Capsules'* article index in the November 2016 issue and at T&C's website, www.tabletscapsules.com.