Reporting CPPs to FDA

Importance of identifying critical process parameters in original submissions to FDA.

It is well known that quality needs to be built into, rather than tested into, a product. The concept gained renewed interest in the pharmaceutical industry with the publication of FDA's "Pharmaceutical cGMP for 21st Century-A Risk Based Approach"[1] in 2004. This was followed by a number of guidelines, most relevant of which were ICH Q8(R2),[2] Q9[3] and Q10.[4]

The term Critical Process Parameter (CPP) became a significant terminology with the publication of ICH Q8(R2), where it was defined as "a process parameter whose variability has an impact on the Critical Quality Attribute (CQA) and therefore should be monitored or controlled to ensure that the process produces the desired quality." Based on the definition, it is imperative that during the development of the manufacturing process, critical process parameters will be identified and controlled appropriately, to assure the robustness of the process, consistency of the product quality and life cycle management. However, there are many occasions where sponsors fail or incorrectly identify CPPs in their process.

The definition of CPP in ICH Q8(R2) indicates that a parameter should be considered critical when its variability can affect the CQA of a product. However, neither ICH Q8(R2) nor related publications indicate the amount of impact that would lead one to consider a process parameter as critical. Thus, a strict interpretation of this definition has sometimes led to extremes in the industry. There are some manufacturers who have considered every process parameter that impacts a product attribute as "critical," irrespective of whether the impact is significant or minimal. This undesirable practice adds unnecessary workload for the manufacturer.

For the Agency, labeling of all process parameters as critical has the same effect as considering all of them, "non-critical," as there is no way to evaluate the impact of these parameters on CQAs during commercial manufacturing. Also, this leads to increase in time invested in reporting and reviewing of post approval changes. On the other hand, there are sponsors who have considered none of the process parameters as "critical"; they have argued that when process parameters are controlled appropriately, they assure that the CQAs are met and are thus not "critical." This does not help either.

While a sponsor may have done significant work to mitigate risks related to the process parameters, criticality of a process parameter is not a standalone determination and depends on other inputs in the unit operations and also scaling up. Thus, by failing to define a process parameter as critical when it should be so defined, one may lose sight of how changes in this parameter may affect the downstream operations or how an unexpected change in the input material may affect it. The Agency has been making significant attempts to understand the criticality of process parameters in the original submission for several years. FDA Guidance for Industry, "Process Validation: General Principles and Practices"[5] recommends reporting a continuum of risk criticality for the parameters. Also, ICH Q9[3] provides the risk management principles which could be used effectively for understanding the severity of risk related to a process parameter and making a decision whether to consider it "critical."

The identification of risk continuum for process parameters can be helpful during evaluation of the manufacturing process. However, providing information regarding mitigation of risk related to a CPP does not always render it non-critical. It is desirable that the knowledge related to criticality of a parameter be retained in the original submission, even when the risk is alleviated. This can also help with cGMP inspections and life cycle management of the product. It assists in allowing the FDA to be cognizant of the kind of changes in the process parameters which could reintroduce the "risk" related to the unit operations.

While the inputs of a unit operation comprises the critical process parameters (CPPs) and critical material attributes (CMAs) of the incoming materials, the outputs are comprised of the attributes which may translate to CQAs for the product. The critical material attribute or CMA,[6] which is not defined by ICH Q8(R2), is comprised of the physical, chemical and biological attributes of an input material which may affect the CQA of a product. The assurance of a consistent output of a unit operation is an interplay of CPPs and CMAs, and variability in either of these could change the output, and thus, CQA of a product. Thus, when a sponsor reports that a "critical" process parameter is non-critical due to process knowledge or de-

Aloka Srinivasan, Ph.D.
Lachman Consultant Services

Aloka Srinivasan, Ph.D. is Vice President, Regulatory Practice at Lachman Consultants who brings more than two decades of experience in the pharmaceutical industry, including nine years of progressive experience with the U.S. FDA in the Office of Generic Drugs. She provides strategic guidance to applicants in regulatory and chemistry, manufacturing and controls (CMC) for drug products and drug substances at all stages of development and for all types of regulatory submissions.

> "The defining of appropriate CPPs also has an impact in the life cycle management of a product."

velopment studies, there is risk that it is not re-evaluated if CMAs or other aspects of the process change post approval and lead to product or process failure.

When CPPs are not identified in the original submission, FDA has asked numerous questions regarding the manufacturing process, impact of variabilities in the CMAs and process parameters, control strategy based on these variabilities, basis of verification of the ranges proposed for the process parameters and the link between the variability of any of the process parameters and CQAs.[6]

The two examples of Pharmaceutical Development published by FDA[7,8] have mentioned the importance of defining CPPs of a process. Also, as stated in FDA Perspective: Common Deficiencies in ANDAs (Part 4),[9] several of the common deficiencies have their root in establishing approprial CPPs in unit operations. The CDER Mapp 5015.10, Chemistry Review of Question-based Review (QbR) Submissions[10] has several questions related to evaluation of criticality of process parameters. Also, the importance of CPPs was emphasized in briefing information and presentations for FDA's Advisory Committee Meeting of September 20, 2018 related to Pharmaceutical Science and Clinical Pharmacology,[10] where FDA announced plans for implementation of the Knowledge aided Assessment and Structured Application program (KASA) for review of quality of ANDAs, BLAs and NDAs. This indicates that the Agency is expecting sponsors to provide the information regarding CPPs in their original submissions.

The defining of appropriate CPPs also has an impact in the life cycle management of a product. With the implementation of ICH Q12,[11] FDA is expecting sponsors to provide "established conditions" related to the product and process, for better management of the lifecycle of a product. The FDA Guidance for Industry, "Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products"[12] provides several elements of the control strategy including process parameters, which may be considered as "established conditions."

When ICH Q12 and FDA guidance are fully implemented, FDA is expected to stress the importance of understanding and identifying CPPs for a process and control strategies which mitigate the risk related to these parameters. This way, FDA may be able to determine if the CPP may or may not be an established condition. Sponsors are expected to identify the CPPs in the original submission and discuss the alleviation of the risk related to these parameters. If a CPP is considered an established condition, any changes in the range may have to be reported to the Agency. Alternatively, based on experience and knowledge gained during commercial manufacturing, if a CPP, originally defined as an established condition, is no longer needed to assure the process performance or product quality, a sponsor can remove it with adequate justification through supplements and annual reports. However, for all of the above to be possible, the CPPs need to be identified in the original submission.

The lack of information related to CPPs in a dossier has led to extensive inquiries from FDA, which have ended in CRLs (complete response letters) and extended the review time of applications. Also, when cited in IR (information request) letters, these questions have time and again led to hasty responses and establishment of ranges based on limited data. These in turn have caused problems with process validation and scale up efforts. Pink Sheet article, "2017 Complete Response Letters: Fewer Than 2016, Still More Than Years Past"[13] indicates that though the number of CRLs were less in FY 2017 compared to FY 2016, the number of quality related CRLs in that respective timeframe increased.

The appropriate risk analysis related to CPPs have affected the Pre-Approval Inspection (PAI) process. To strengthen the FDA inspection process, Dr. Janet Woodcock, Director, CDER, FDA has frequently talked about the Integrated Quality Assessment,[14] where the reviewer works with the inspectors to consider all elements that create risk in a product. As part of this initiative, many reviewers are accompanying the inspectors during the PAI. Lack of adequate information in the dossier regarding control strategies and CPPs carry the risk of triggering this kind of joint inspection which could lead to additional observations by the reviewer and inspector, thus delaying the approval process.

In view of the current trends in FDA, the best practice for a sponsor is to start providing appropriate CPPs in the original submission of the NDAs/ANDAs/BLAs, based on their process understanding. This is expected to mitigate unnecessary risks of delay in approval due to CRLs and/or FDA-483 observations during the PAI inspection. **CP**

For a full list of references please visit the online version of this article at ContractPharma.com.