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PQRI-FDA Workshop Summary on Process Drift

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FDA's Office of Compliance and Office of Pharmaceutical Science, both part of the Center for Drug Evaluation and Research (CDER), and the Product Quality Research Institute (PQRI) co-chaired a workshop for industry on process drift in December 2010, in North Bethesda, MD. This paper summarizes the discussions and feedback obtained during the meeting.

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Note: The views presented in this summary article do not necessarily reflect those of FDA or of the organizations in which the authors are employed.

FDA's Office of Compliance and Office of Pharmaceutical Science, both part of the Center for Drug Evaluation and Research (CDER), and the Product Quality Research Institute (PQRI) co-chaired a workshop for industry on process drift in December 2010, in North Bethesda, MD. The workshop was well attended by participants representing industry, academia, and CDER. The program received high marks for its content and quality. The presentations were deemed relevant and compelling, with many examples illustrating a life-cycle approach to active monitoring and improving manufacturing performance. Both APIs and myriad pharmaceutical dosage forms were discussed. There was general agreement that this workshop deserves additional exposure. It was proposed that PQRI offer additional programs in the US and abroad, and publish a summary of the workshop. This article is intended to meet the latter objective.

Defining process drift

Process drift in the manufacture of an API or a drug product was defined by workshop attendees as:

An unintended, unexplained or unexpected trend of measured process parameter(s) and/or resulting product attribute(s) away from its intended target value in a time-ordered analysis over the lifetime of a process or product.

In many instances, process drift is the consequence of variation in a variety of process inputs, including raw materials, manufacturing personnel, and machine (man-machine) interactions or processing conditions. In some cases, the testing of materials or measurement of process parameters may also experience drift. As an example, process drift is occurring when a unit operation of a manufacturing process moves toward the edge of its acceptable process ranges. Consequences can ultimately include significant variability in drug release, content uniformity, assay, or other product attributes. Unacceptable variation during processing may lead to problems with consistency of in-process output, finished-product quality at release, or increased risk of failing specification before shelf-life expiry. It is important to understand, monitor, and control process drift so that action can be taken before it impacts the patient.

Understanding the major sources of variation is essential to the design and control of robust processes in the manufacture of pharmaceuticals. Over time, a component or process may drift from its target due to intrinsic or extrinsic factors. These factors may initially be unknown or considered to be of lesser significance. Failure to adequately control processes and prevent defects can pose risk to patients/consumers, affect product availability, and yield undesirable regulatory and business outcomes.

The objectives and scope of the FDA-PQRI workshop included:

- Discussion of a life-cycle approach to monitoring manufacturing performance that assures prompt detection and correction of meaningful variation
- Exploration of technological and management system approaches to better identify, measure, and control process variation and mitigate undesirable product variability

- Discussion of the impact of process drift on product performance, safety, and efficacy.

Preventing process drift

Prevention of process drift and continual improvement was a central theme of the workshop. In addition to the quality benefits, workshop participants discussed important business efficiencies gained from improving quality, such as reduction in inventories, unexpected shutdowns, operational costs, and capital expenditures. Trend monitoring is an important preventive program of a drug manufacturer to identify impending issues and allow time to investigate and resolve the problems before there is an impact on the patient. Statistical Process Control (SPC) and other time-ordered analyses can be used, ideally in real-time or shortly after completion of the process stage, to identify undesirable variation and enable appropriate action. Such early-warning systems enable detection of intra-batch and inter-batch process drift in a pharmaceutical operation and are an integral part of a 21st-Century quality system. Suitable quality standards for APIs, excipients, container-closure systems, and drug products must be designed, implemented, monitored and periodically evaluated by persons involved in pharmaceutical manufacturing and quality control/quality assurance, including management. Senior management's role was strongly emphasized as central to an organization's success at achieving proactive quality assurance rather than reactive quality control.

Modern technology and process control approaches were discussed. Detection, diagnosis, and enhanced upstream control of process variables can be modeled and process trajectory more tightly measured and controlled to ensure consistent material output. With this enhanced quality information for each unit operation, intelligent control systems can be employed to provide dynamic feedback for larger manufacturing process improvement efforts. This improved knowledge will enable the impact of changes to the product or process to be predicted better so that the undesirable impact on product quality and stability can be prevented. Ultimately, enhanced process information will facilitate a state of process

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control (including continuous process verification) throughout the life cycle and yield drug quality benefits to both industry and consumers.

When robust systems are not implemented and capable tools are not used to prevent process drift, resulting manufacturing problems may include: low product yield, batch delays, ingredient and packaging variability, batch failures, product quality-related clinical failures, investigations, recalls, product seizures, injunctions, and consent decrees.

Detection and resolution of process drift was discussed for APIs, key excipients, and a variety of dosage forms (solid orals, transdermals, topicals, injectables, metered-dose inhalers and dry powder inhalers). The impact of alternate source qualification for drug product ingredients and packaging components was also included. The effect of process drift on specifications and shelf-life was addressed. In addition, participants discussed proper supplier management, product quality monitoring and control systems (e.g., PAT), corrective and preventive action (CAPA) programs, and quality-by-design (QbD) approaches. Each approach was considered an integral piece to establishing and maintaining a stable manufacturing system.

Breakout sessions

Breakout sessions among participants focused on:

- The definitions and terms for describing process variation and process drift
- The most frequent causes of variation in pharmaceutical manufacturing
- Current strategies for monitoring and detecting process variability
- Evolutions in industry management approaches and the regulatory environment that could promote more proactive process improvement throughout the product life cycle
- Impact of process drift on product bioavailability, safety, and efficacy.

The following section summarizes key outcomes of the breakout sessions.

Workshop participants recognized “process drift” as an “unintended, unexplained, or unexpected trend of measured process parameter(s) and/or resulting product attribute(s) away from its intended target value in a time-ordered analysis over the lifetime of a process or product.”

When a substantial number of errors that occurred in pharmaceutical manufacturing were analyzed over a specified period, their distribution was 40% due to recurring human errors, 30% due to recurring process errors, and 30% nonrecurring errors, as stated by one of the speakers during the workshop. Human errors are due to inadequate training, poorly understood standard operating procedures and processing parameters, lack of skill sets and procedural control, and inadequate resources. Other sources are inadequate change management and risk management. Unsuitable equipment, deficient preventive maintenance, and inadequate equipment calibration also lead to movement away from the normal process variability. Inadequate understanding of the inherent variability in and inappropriate characterization of excipients, APIs, and other components can lead to unacceptable process variation and can be one of the most complex areas to track during the life cycle of a pharmaceutical product.

Scientific rationale is needed to select variables on which to focus most when monitoring process drift. For raw materials, the certificate-of-analysis (CoA) testing alone is insufficient to determine excipient variability. In comparison with commonly used univariate analyses, use of multivariate analytical methods for assessing properties of raw materials, in-process materials, and finished products by modeling relevant material attributes and process variables can support increased quality assurance. However, appropriate education, training, and manufacturing process understanding is necessary to properly use these methods. Analytical method drift should also be monitored.

Evolutions in industry management approaches could promote a more proactive process improvement throughout the life cycle of a product. Justification to senior management is necessary to design and implement quality assurance concepts. Workshop participants agreed that upper management

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must support the efforts to assure drug quality and understand the inherent costs of poor quality. Estimation of the cost of failure can provide an indication of the ramifications and support the resources needed. Better metrics are needed to quantify the risk-benefit ratio.

Participants also indicated that the regulatory landscape needs to be more predictable. Some also felt that the time and cost to provide information to the regulators and receive approval for process improvements can be prohibitive.

Process drift has the potential to affect product performance for all types of dosage forms. More meaningful analytical tools for understanding and detecting process drift are needed. Identification and use of improved input material measurements and process information are necessary to improve the likelihood of alerting a manufacturer to process variability that may impact product quality, including drug bioavailability. For example, to date, the best *in vitro* marker available to industry for drug bioavailability is dissolution. Even when *in vitro-in vivo* correlation is not conclusively established, significant emerging changes in product quality and manufacturing consistency are detected by testing a compressed tablet for tablet disintegration and drug dissolution.

Overall, the participants felt that further work is needed to develop better methods that recognize and enhance understanding of the effects of process drift on product quality and product performance.

Conclusion

Feedback obtained from FDA-PQRI workshop attendees through a post-event survey has been positive. The topic of enhancing life-cycle management of process drift should be elaborated at future workshops, including discussion of advancements and innovations in manufacturing technology that allow for dynamic process control.

Additional reading

1. PQRI-FDA Workshop on Process Drift program, www.pqri.org/pdfs/processdrift_finalprogram.pdf.
2. PQRI-FDA Workshop on Process Drift summary, *Gold Sheet*, www.pqri.org/workshops/ProcDrift/imagespdfs/DrugMakers_Goldsheet_article.pdf. **PT**

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