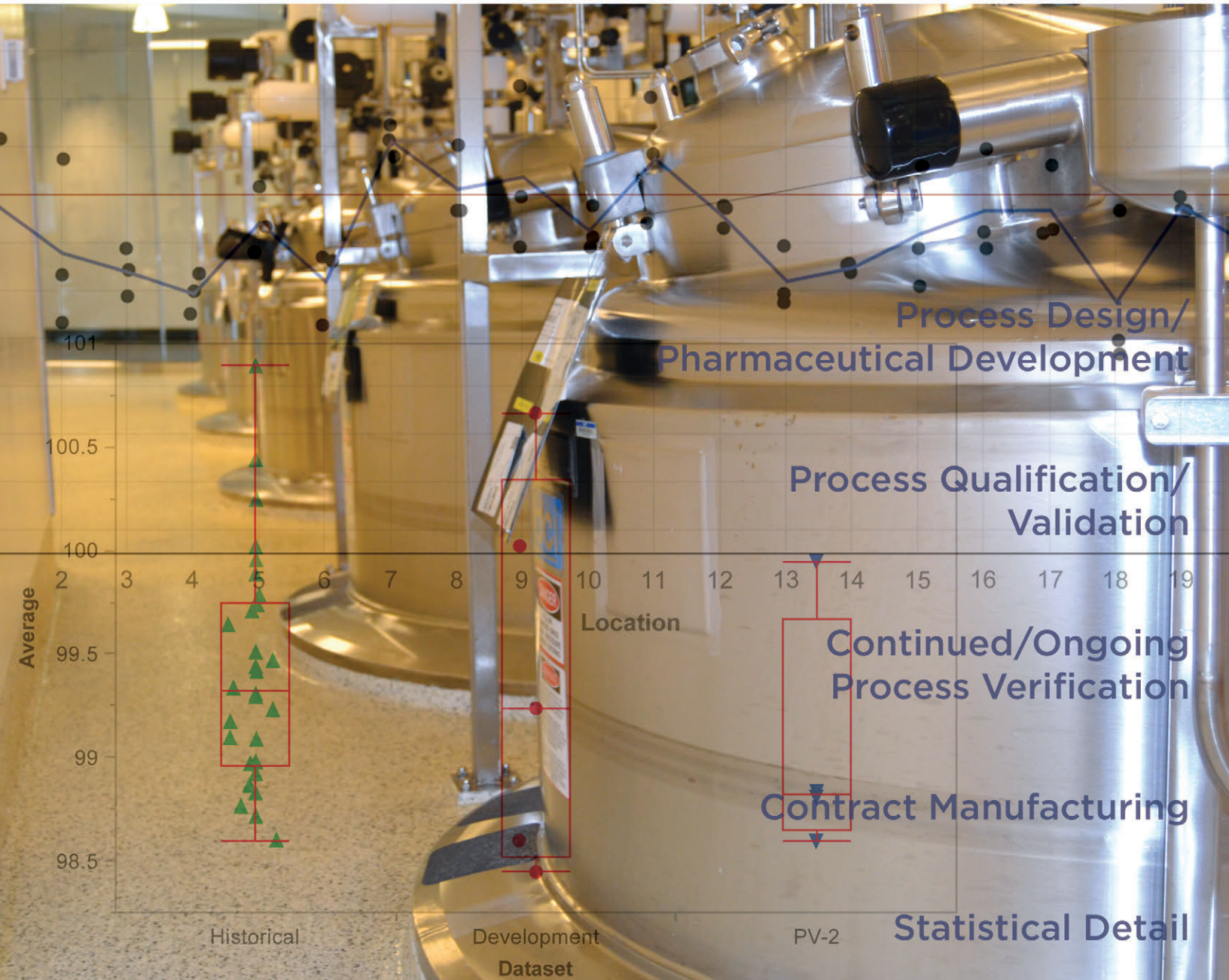
ISPE®

GOOD PRACTICE GUIDE:

Practical Implementation of the Lifecycle Approach to Process Validation



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Foreword

During my tenure at the FDA, I presented at many industry conferences on various topics, but few represented such significant change and improvement as those which culminated in the lifecycle approach to Process Validation (PV). In 2002, FDA launched the Pharmaceutical Quality for the 21st Century initiative aimed at modernizing pharmaceutical manufacturing using sound science and risk-based approaches. ICH shortly thereafter also embarked on its vision for pharmaceutical quality and set forth ICH Q8, Q9, Q10, and Q11.

- Q8 Pharmaceutical Development (August 2009)
- Q9 Quality Risk Management (November 2009)
- Q10 Pharmaceutical Quality System (June 2008)
- Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) (May 2012)

A fundamental principle to ensure product quality is PV. In the past, interpretation of FDA's Compliance Policy Guide (http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074411.htm), which addressed process validation and the subject of guidance from FDA over multiple versions, there had been the impression that three commercial PV batches were almost always enough to ensure a robust and consistent process. This guide was updated in 2004 to facilitate understanding of requirements to bring products to market, especially when extensive process development efforts and large numbers of PV batches are not practical, e.g., orphan drugs.

Over time in FDA and in other international guidances, three batches had become the standard to demonstrate a validated process. With the lifecycle approach, efforts were made to bring PV into the 21st Century - to provide scientific evidence to justify going from development to commercial manufacturing while maintaining the desired process control over the product's lifecycle. The intent was also to capture modern manufacturing methods using enhanced approaches, e.g., continuous manufacturing.

In 2011, the 1987 Guideline on General Principles of Process Validation was replaced, reflecting the modernization efforts for pharmaceutical quality initiated by FDA and in the international arena. Of the regulatory guidances issued to date, the FDA Guidance for Industry: Process Validation: General Principles and Practices of January 2011 contains the most detail in regard to expectations for the three stages of the lifecycle approach to PV, but was followed internationally by several other impactful guidances and regulations, outlined below.

In February 2014, EMA published its "Guideline on process validation for finished products – information and data to be provided in regulatory submissions." The scope of this document covered:

- Human medicinal products
- Veterinary medicinal products
- Biological products

A companion guideline "Guideline on process validation for the manufacture of biotechnology-derived active substances and data for inclusion in the regulatory submission" was published in April 2014.

These documents introduced the concepts of science and risk-based validation to Europe via:

- Process evaluation (Stages 1 and 2)
- Process verification (Stage 3)

The EU PV guidance sets out three approaches for PV:

- Traditional (three batches)
- Continuous process verification
- Hybrid (three batches or Continuous in different steps of the process)

Additionally, these guidance documents refer to GMP requirements for PV in Annex 15: Qualification and Validation to the EudraLex Volume 4 (Good Manufacturing Practice Medicinal Products for Human and Veterinary Use). This guidance was published for comment in March 2015 and became operational in October of the same year concurrent with its publication by PIC/S. Unlike the FDA guidance; Annex 15 also contains specific validation approaches to:

- Transport verification
- Packaging qualification
- Utilities qualification
- Test method validation
- Cleaning validation

The EMA guideline on PV for finished products underwent a minor update in November 2016.

With these modern approaches to pharmaceutical development and manufacturing and the advancement of the concept of PV to a lifecycle approach, ISPE's Product Quality Lifecycle Initiative (PQLI®) has been providing the technical underpinnings to develop the necessary education, training, and discussion papers to pharmaceutical professionals engaged in all facets of pharmaceutical development, commercialization, and manufacturing. This *Good Practice Guide: Practical Implementation of the Lifecycle Approach to Process Validation* brings together an excellent reference providing the technical and scientific detail needed to lead PV through scientifically sound development to robust reliable processes, ensuring the continued supply of quality medicines to patients.

An expert group of volunteers with manufacturing, quality, technical development, and statistician backgrounds has brought this effort to the point of providing this Guide to our ISPE members. It covers a wide variety of manufacturing types including small and large molecule, active pharmaceutical ingredients (including intermediate steps), solid oral dosage forms, sterile drug product, etc.

This Guide will be an invaluable reference bringing together many of the efforts to date for use in your daily activities and as an underpinning to ISPE's ongoing education and training in this area.

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1 Introduction

Between 2004 and 2009, ICH published guidance documents Q8 (Quality by Design – Pharmaceutical Development) [1], and Q9 (Quality Risk Management) [2], which describe the science and risk-based approach to the development of pharmaceutical products. These guidances represented a paradigm shift in development, commercialization, transfer, and management throughout the product lifecycle.

The science and risk-based approach to Process Validation (PV) leverages information and knowledge from product development activities to make certain patient requirements are translated into product attributes. This requires that suitable manufacturing processes are defined with a control strategy that reliably ensures these attributes are met. Regulatory authorities worldwide have published revised guidances for science and risk-based approaches to be applied to PV, which presents a significant change to the way validation had been conducted.

PV demonstrates manufacturing control strategy adequacy and robustness and provides ongoing assurance that the process remains in control. It is defined in the 2011 FDA PV Guidance as [3]:

> *"…the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process validation involves a series of activities taking place over the lifecycle of the product and process."*

Other regulatory authorities have similar definitions for PV although terminology may differ.

This new (enhanced) approach to PV encompasses three stages, illustrated in Figure 1.1, as compared to the traditional or historic approach. The science and risk-based approach combines product development knowledge with a structured process performance and product quality monitoring system to provide for validation throughout the product lifecycle.

Figure 1.1: Process Validation Overview – Process Validation Lifecycle – the Enhanced Approach