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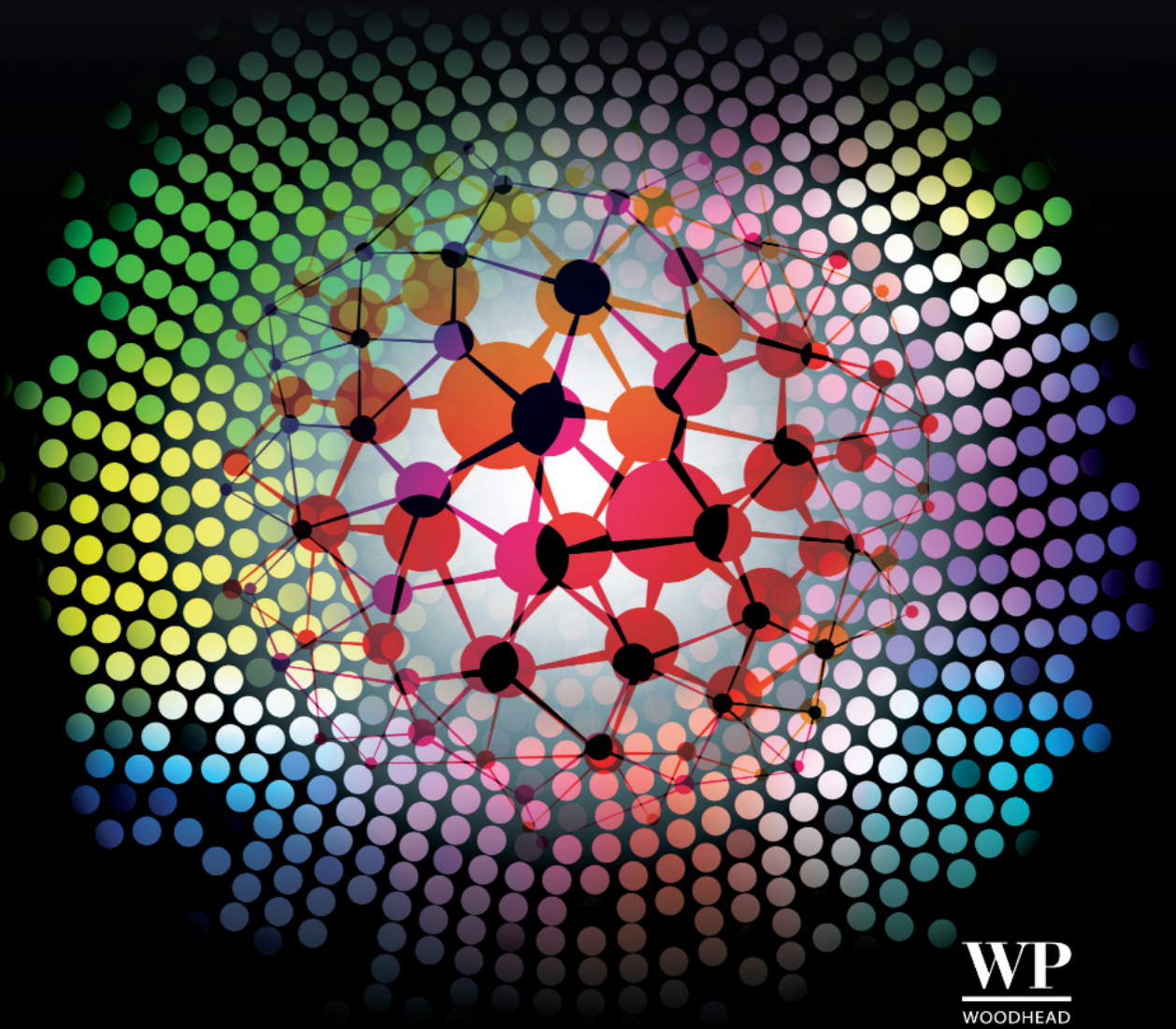

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Problem solving and training strategies for success in the pharmaceutical and life science industries

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List of abbreviations

ADDIE	Analyze, Design, Develop, Implement, Evaluate
AE	Adverse Event
ANOVA	Analysis of Variance
API	Active Pharmaceutical Ingredient
CAPA	Corrective Action and Preventive Action
CEO	Company Executive Officer
CFE	Certified Fellow Employee
CFR	Code of Federal Regulations
cGMP(s)	Current Good Manufacturing Practice(s)
CLIA	Clinical Laboratory Improvement Amendment
CPR	Cardiopulmonary Resuscitation
CQU	Quality Complaint Unit
DEG	Diethylene Glycol
DIL	Dear Investigator Letter
EDMS	Electronic Document Management System
EM	Environmental Monitoring
ESI	Equipment-Specific Instructions
FDA	(US) Food and Drug Administration
FIR	Final Investigation Report
GCP(s)	Good Clinical Practice(s)
GLP(s)	Good Laboratory Practice(s)
GMP(s)	Good Manufacturing Practice(s)
GXP(s)	This acronym includes GCPs, GLPs, and GMPs
HCT/Ps	Human Cells, Tissues, and Cellular and Tissue-based Products

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HPCL	High Performance Liquid Chromatography
HPV	Vaporized Hydrogen Peroxide
HR	Human Resources
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IQ	Installation Qualification
IRB	Institutional Review Board
ISO	International Organization of Standardization
ISPE	International Society for Pharmaceutical Engineering
ITP	Individual Training Plan
JITT	Just-in-Time Training
JSA	Job Safety Analysis
KTA(s)	Knowledge Transfer Assessment(s)
LMS	Learning Management System
LOTO	Lockout/Tagout
MedDRA	Medical Dictionary for Regulatory Activities
MSDS	Material Safety Data Sheet
NDA	New Drug Application
NEO	New Employee Orientation
NoE	Notice of Event
OJT	On-the-Job Training
OOS	Out-of-Specification
OSHA	Occupational Safety and Health Administration
OQ	Operational Qualification
PCA	Peanut Corporation of America
PDP	Planned Deviation Protocol
PPE	Personal Protective Equipment
PQ	Performance Qualification
PQC	Product Quality Complaint
PQLI	Product Quality Life-cycle Implementation
QA	Quality Assurance
QC	Quality Control
QMS	Quality Management System

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RCA	Root Cause Analysis
RCT(s)	Randomized Clinical Trial(s)
R&D	Research and Development
ROI	Return on Investment
SAE	Serious Adverse Event
SDA(s)	Skill Demonstration Assessment(s)
SISPQ	Safety, Identity, Strength, Purity, Quality
SME(s)	Subject Matter Expert(s)
SOJT	Structured On-the-Job Training
SOP	Standard Operating Procedure
TTT	Train-the-Trainer
UAE	Unexpected Adverse Event

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About the author

Gordon Welty, PhD, has over twenty-five years of professional experience in program development and the management of organizational change. Welty's doctorate is from the University of Pittsburgh. He has taught at universities at home and abroad, including American University, Temple University, and the universities of Akron and Toronto. He was named Professor Emeritus at Wright State University in 1998. He is currently Lecturer in Social Science at Adelphi University.

Welty was recruited to develop, rollout, and manage the GMP Train-the-Trainer program as CAPA for Schering-Plough's consent decree in 2003.

Welty's writings have appeared in such scholarly publications as *Academy of Management Journal*, *International Sociological Review*, *Journal of Value Inquiry*, *Metroeconomica*, and *The Monist*, as well as a number of anthologies. He was the recipient of the Institute of Validation Technology's "Author of the Year" Award in 2008, 2009, and 2010. Welty received his Certificate in Journalism from the International Journalism Institute in Budapest in 1989. His op-eds and journalism have been published in the popular press at home and abroad.

Contact details
Gordon Welty
Email: *gwelty@wright.edu*

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1

Framework for continuous improvement

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Abstract: This chapter considers occasions that lead to the continuous improvement of manufacturing processes and programs in the life sciences industry, and to the revision of SOPs. Several groups of stakeholders in the sphere of FDA-regulated industry are identified. Each of these groups tends to be associated with particular kinds of observations, observations of various deviations from the anticipated manufacturing process and product. These observations initiate an investigation and revising process that varies in emphasis but that has an underlying logic. An observation is typically escalated, triaged, and can become the basis of an investigation and RCA. At the conclusion of the investigation, programmatic remediation can be proposed in the form of corrective actions and preventive actions, and may ultimately lead to the revision of a procedure. A diligent approach to revision promotes the continuous improvement of the manufacturing process.

Key words: adverse event, change control, controlled document, corrective action, customer quality complaint, deviation investigation, good management practice, management notification, Notice of Event, preventive

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action, regulatory inspection, SISPQ, standard operating procedure, stakeholders.

1.1 Introduction

There are events and situations that – when observed and acted upon – initiate the revision of processes and procedures addressed by good manufacturing practices (GMPs) in a regulated industry such as that covered by the US Food and Drug Administration (FDA) or other global regulatory agencies. These events and situations can lead to two kinds of revision of GMP processes. They can be either *reactive interventions* such as corrective actions, or *proactive interventions* such as preventive actions. An example of a proactive intervention would be the organization's response to tracking and trending data that suggest critical action points will soon be exceeded. Another example of proactive intervention would be an organization's response to a "close call," where a deviation did not actually occur.

In either case, reactive or proactive intervention, systematic pursuit of revision leads to continuous improvements.

Events and situations do not generate the intervention by themselves. The key terms here are "when observed and acted upon," focusing attention on the major groups of stakeholders that can initiate the chain of events leading to the change. The persons occupying each of these stakeholder roles must first observe, then act, to occasion the intervention.

There are five major groups of these stakeholders. These five groups make up a map of the overall sphere of the regulated life sciences industry. Each represents a different facet of regulated industry, including the following:

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1. operational staff and their supervisors;
2. quality unit auditors;
3. regulatory investigators;
4. health care providers;
5. patients and other health care consumers.

In brief, operational staff manufacture the regulated product, be it a drug, medical device, nutritional supplement, etc. The quality auditors function independently to monitor the activities of operational staff as well as the quality attributes – the Safety, Identity, Strength, Purity, and Quality (SISPQ) of the product. Agency investigators in turn regulate the activities of both operational and quality staff. Health care providers prescribe the product, and patients utilize the product.

Any member of these groups can make an observation that may bring about an investigation and RCA. Consider several illustrative observations:

- A forklift operator raised the forks too high and damaged a fire sprinkler head. The water was under high pressure and it not only flooded the area but cascaded down to the floor below, threatening to inundate production areas. After an engineer shut off the water supply, operational staff escalated this event to management.
- The quality unit of a FDA regulated blood center reported an increase in the number of BacT Positive samples, which might be indicative of contamination with tuberculosis bacteria. The samples turned positive over the weekend. An investigation was initiated.
- FDA 483 *Observation to Genzyme* dated 13 November 2009, for example, pointed out that Genzyme's:

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> . . . Investigation AIR 1517 dated 21 June 2007 was opened because HEPA filters in the filling suite failed routine recertification. The investigation found metal particles embedded in several of the HEPA filters. However, no route [*sic*] cause was determined for the source of the metal contamination found in these filters.[1]

- FDA MAUDE *AE Report on Genzyme Biosurgery's Synvisc Injection* dated 4 August 2008: "The [health care provider] assessed the relationship of the events – swelling both knees and right knee effusion – to synvisc as probable. He assessed the relationship of the event – allergic reaction to synvisc – as likely."[2]
- McNeil Consumer Healthcare recalled bottles of Tylenol eight-hour caplets after some consumers complained of a musty or moldy odor in the product.[3]

The outcome of an investigation can be followed by the development and execution of corrective actions and preventive actions (CAPA). The logic of this investigative and revising process may be more or less explicit in the various regulated industries, but the underlying logic is the same.

Briefly put, a CAPA can identify several kinds of remediation for a given observation. Some remediation implicates the revision of a standard operation procedure (SOP); other remediation does not. This chapter focuses on the range of intervention and remediation, giving special attention to those that lead to the revision of procedures.

Following an initial section of this chapter that addresses the function of SOPs and the revision of life-cycle documents, the second section discusses the routine review of procedures. This set of routine practices should be juxtaposed to the set

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of exceptional practices. Thus routine practices can be taken as a baseline for the exceptional practices that are addressed in the remainder of this chapter. The third section addresses the two kinds of internally-based observations that can initiate an intervention and thereby the revision of SOPs: employee notification to supervision and quality (internal) audits. The fourth section discusses the three types of externally-based observations that may initiate an intervention and thereby the revision of a SOP: regulatory inspections, adverse event (AE) reporting, and customer quality complaints.

1.2 Procedures and change

Controlled documents such as SOPs, batch records, manufacturing orders, packaging orders, etc. provide guidance for performing tasks. For brevity's sake, all these controlled documents are referred to herein as "procedures" or "SOPs." The procedure identifies the tasks, the environmental and organizational setting for task performance, the resources that make up the prerequisites to each task, the sequencing of the tasks within a given process, the personnel responsible for completing the tasks, and the standards that define the satisfactory completion of the tasks. As David Peterson states:

> The purpose of an SOP is straightforward: to ensure that essential job tasks are performed correctly, consistently, and in conformance with internally approved procedures. Clearly, employees' correct, consistent performance of essential job tasks is as much a business and quality issue as it is a regulatory requirement.[4]

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Of course, the use of SOPs in manufacturing in the life sciences industry is also a regulatory requirement. FDA has stipulated, "There shall be written procedures for production and process control designed to assure that the drug products have the SISPQ they purport or are represented to possess." Furthermore, "such written procedures shall be followed."[5] FDA has stated similar predicate rules for written SOPs for many of the areas under its jurisdiction, as displayed in Table 1.1. FDA has even stipulated predicate rules for written SOPs that apply to itself, *Good Guidance Practices*.[6]

What are some of the consequences of the absence of written procedures?

- Without SOPs there is confusion about what the task is and where the task should be performed.
- Without an SOP the task performance will be poorly resourced – either under-resourced or wastefully resourced. In either case, task performance is more costly, since the

Table 1.1 FDA predicate rules for written SOPs

Regulated Area	Regulation	Predicate Rule
Biologics	21 CFR 600.80	Post-market AEs
Food	21 CFR 179.25	Food irradiation
GCP	21 CFR 56.101	IRBs
GCP	21 CFR 310.305; §314.80	Post-market AEs
GLP	21 CFR 58.35	QA unit
GMP	21 CFR 211.186	Control records
GTP	21 CFR 1270.31; §1271.180	Good tissue practices
HAACP	21 CFR 120.11	Calibration
Medical Devices	21 CFR 812.25	Investigational plan

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under-resourced case may require rework, and the over-resourced case may require cost recovery.

- The sequencing of tasks may go awry without an SOP – a task that must precede a task may be omitted, or a task that depends upon another task may be performed too soon. Either of these could threaten the integrity of the entire regulated process.
- In the absence of an SOP, personnel may be confused about who is responsible for each task. Tasks may not be successfully performed if there is no one responsible for them, or if two or more employees are responsible for them.
- Without an SOP there are no standards to define the satisfactory task completion.

SOPs are not set in stone, once and forever. Business process and regulatory requirements for using SOPs incorporate the necessity of revising procedures. The revision process provides an opening for continuous improvement insofar as the changes represent improvement. FDA predicate rules call for not only "written procedures" that "shall be followed," but the predicate rules also stipulate "written procedures, including any changes."[7]

There are several aspects to this issue of "changes." First, an SOP is a controlled document, so any change in the associated process must be documented in conformity with the organization's change control process. Second, the FDA predicate rules stipulate that the GMPs must be "current" (i.e., cGMPs), so that changes in the associated process or practices must be captured in the procedure in a timely fashion. Third, technological change is ubiquitous in the life science industry, so there will always be the necessity of revising SOPs as an aspect of business process as well as a regulatory requirement.

Because SOPs must be and are constantly revised in a controlled fashion, it will prove useful to identify the various kinds of events and situations that may call for the revision of procedures. Neither an event nor a situation automatically calls for intervention; these must be labeled as "events or situations of interest" by an appropriate administrative procedure.

There are two fundamental kinds of occasions for revision: routine review of life-cycle documents and revision due to observations of a non-conformance, etc. In turn, there are five main kinds of observations – those that follow from escalated events, from internal audits, from regulatory (FDA) inspections, from AEs, and from customer quality complaints. These five kinds of observations correspond to the five stakeholder groups identified previously, and are displayed in Table 1.2.

A complex decision process lies between observation and intervention. Any one of the five kinds of observations may bring about an investigation. An observation is typically escalated, triaged, and may or may not become a record of interest in the organization's quality management system (QMS). It is the QMS record that may or may not become the basis of an investigation and RCA. The record can also become part of a set of similar records that can be tracked

Table 1.2 **Correspondence between roles and observations**

Major Roles	Kinds of Observations
Operational staff and supervisors	Escalated events
Quality unit auditors	Internal audits
Regulatory investigators	Form 483 observations
Healthcare providers	Adverse events
Patients	Customer quality complaints

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and trended. If necessary, they can be investigated further. The conclusion of an investigation can be followed by the development and execution of CAPA. These elements are displayed in Figure 1.1.

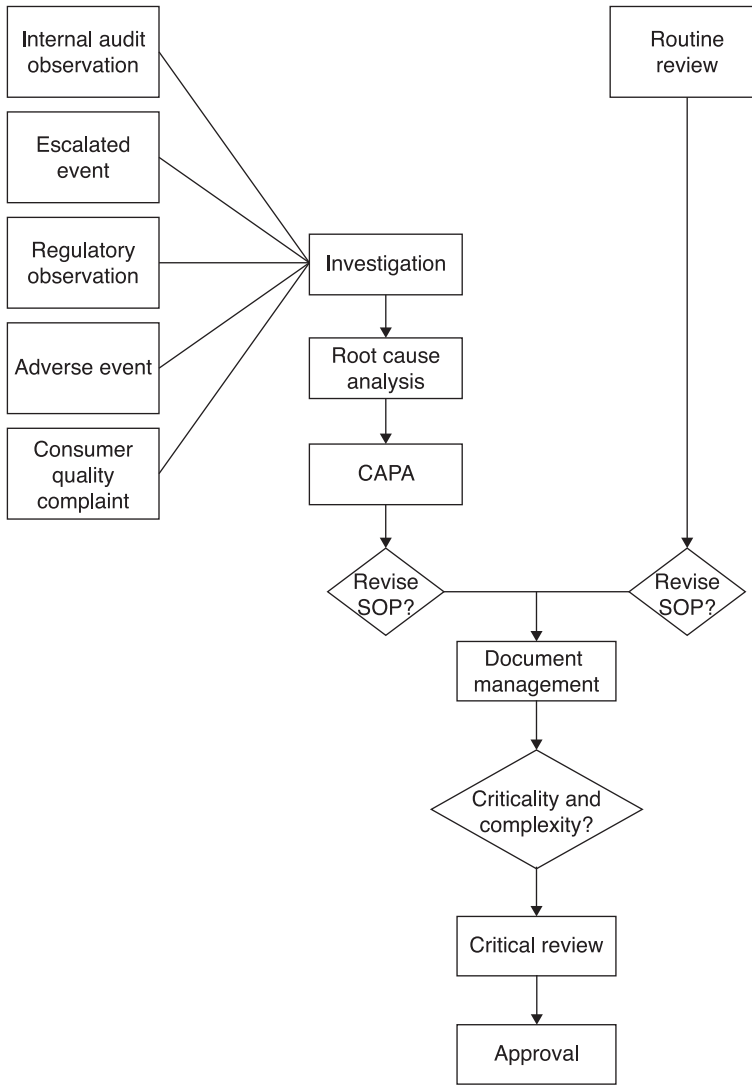

Figure 1.1 Structure of investigations and remediations

The logic of this investigative and remediation process may be more or less explicit; it is quite explicit in the case of GMPs. It is less explicit in other regulated areas. The underlying logic remains.[8]

Even if an observation does, on occasion, lead to the re-engineering of the GMP process, it does not necessarily lead to the revision of a procedure. A CAPA can identify several kinds of remediation for a given observation (e.g., business process redesign, risk mitigation, organizational development programs, leadership development initiatives, training intervention, etc.). Some intervention implicates the revision of an operational SOP; other intervention does not.

This section has discussed the function of SOPs and the impact of change on life-cycle documents. It makes the point that change opens the way for continuous improvement of GMP processes in the life sciences industry. The next section addresses the routine review of life-cycle documents.

1.3 Routine review of life-cycle documents

The routine review of life-cycle documents takes place on a regular schedule, typically every two years (biennial review) or every three years (triennial review). Some controlled documents, for example manufacturing orders, are continuously reviewed. At the beginning of the life-cycle, the specific version of the SOP is approved by management and quality assurance (QA) and is then implemented or "reissued." Once implemented, like any controlled document, the SOP remains subject to change control. Either it will be unchanged during the life-cycle of that version, or it will be changed according to the organization's change control

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procedure. If the SOP is unchanged, it will be diligently executed during the remainder of its life-cycle. If problems of execution occur, it will still be diligently executed until it is appropriately changed.

Should problems of execution become apparent during the life-cycle of the current version, there are two options. If the problems are not critical (i.e., presenting neither business risk nor quality risk), they can be documented by the business owner (or management in any impacted area) and filed for the next routine review. An example of a non-critical problem might be a change of name of an organizational unit that is referenced in the SOP. If the problems are critical (i.e., posing a business risk or a threat to the SISPQ of the product), a planned deviation protocol (PDP) can be prepared according to the organization's change control procedure to revise the current version. The PDP serves as a corrective and preventive action to revise the SOP until the next routine review. As soon as the PDP is implemented, the SOP as revised will be diligently executed during the remainder of its life-cycle.

The elements of the routine review of an SOP are displayed in Table 1.3.

Once these steps have been completed, the SOP can be subjected to a critical review, in light of the complexity and criticality of the associated process. As the next chapter explains, this critical review can take the form of a management review, an SME review, or a step-by-step real-world challenge. Finally, the SOP is approved and implemented.

1.3.1 A different organizational approach

Some organizations take a different approach to the routine review of operational SOPs. Consider the following: an

Table 1.3 The routine review of life-cycle documents

1. Begin the routine review of life-cycle documents such as SOPs by identifying the particular document that is due for versioning up. In the case of biennial review, this involves tracking all SOPs and provisionally tagging those that were implemented two years ago.
2. Accommodate the typical time involved in the document change process. Suppose the amount of time needed to revise an SOP is six weeks. This amount of time is added to the tracking process, so the SOPs that are being tagged are those implemented 25.5 months ago (rather than 24 months ago). This ensures enough time for those SOPs to be revised within their life-cycle.
3. Identify the business owner/author of each of those tagged SOPs.
4. Query that business owner to assess the number and substance of proposed revisions to the SOP that have been gathered over the past two years. If those proposed revisions are neither numerous nor substantial, prepare for a minor revision – sometimes called an "update" – of the SOP. If the proposed revisions are numerous and/or substantial, prepare for a full revision of the SOP.
5. Review the SOP and identify all impacted organizational units. In the case of the proposed update, contact the impacted units, indicate the assessment, and invite inputs to the update. In the case of the full revision, contact the impacted units, indicate the assessment, and propose a cross-functional meeting.
6. Prepare the draft document per the appropriate administrative procedure. If it is only an update, submit for approval (see item # 10 below).
7. List the draft document in the document management schedule.
8. If necessary, facilitate the cross-functional meeting and review the draft document to ensure all impacted areas make their inputs.
9. Revise the draft document to address the comments raised in the cross-functional meeting.
10. Submit the document as revised to the management review process.

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implemented, operational SOP that was due for routine biennial review would be identified. By one administrative procedure (call it "SOP Review Cycle"), an SME was assigned to review the operational SOP. The SOP Review Cycle procedure required the SME to "compare the operational SOP to current practices." If the operational SOP was found not to deviate from "current practices," the SME would prepare a work request for an "updating" of the operational SOP, whereupon its version number would be raised and the next due date for its revision would be stipulated. This "updating" of the operational SOP is not considered to be a versioning up. If the operational SOP was found to deviate from the "current practices," the SOP Review Cycle required the SME to prepare a work request for a "revision" of the operational SOP. Then, by a second administrative procedure (call it "Creation and Revision of Operational Documents"), the operational SOP would be revised and its content brought into accord with the current practices. What is wrong with this picture?

Clearly this organization was not following cGMPs or, presumably, its own written operational procedures. In terms of cGMPs, FDA has stipulated that "written procedures shall be followed." FDA did not suggest that written procedures be followed sometimes, and current practices be followed other times.

In other words, the operational practices are to conform to the written procedures, not vice versa, and moreover "any deviation from the written procedures shall be recorded and justified."[9] This recording and justification process must be timely, certainly not on a two-year cycle. There is the possibility of FDA inspectional observations regarding the failure to follow written procedures. On top of that is the possibility of FDA inspectional observations regarding inadequacy of the organization's investigations and CAPAs.

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Moreover, in the example, this approach to the routine review of life-cycle documents contradicted the organization's change control procedure. That procedure stipulated that for proposed changes to be implemented, an operational SOP had to be appropriately requested, processed, and approved. A proposed change request had to indicate any impact the changes would have on process, material, product, regulatory filings, etc. The request also had to identify activities, responsible parties, deliverables, and time frames and due dates, comprising the proposed changes. Pending the approval of the change request, the current version of an operational SOP was to be executed diligently. There is no easy way to harmonize such contradictory SOPs as the SOP Revision Cycle procedure and the change control procedure.

This section has addressed the requirements for the routine review and controlled change of life-cycle documents such as an operational SOP. An alternate approach to routine review is discussed; however, it was found that the alternate approach posed the threat of FDA inspectional observations. The next section of this chapter examines the occasions for remediation that are due to an internally-based observation. Some of these implicate the revision of an SOP; others do not.

1.4 Intervention due to internal observation

There are two major occasions for remediation because of an internally-based observation that may require the revision of an operational SOP. The first is an observation made by an employee that requires notification to management of a business risk or quality risk. The second is an observation made by an auditor during an internal quality audit.

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1.4.1 Management notification

The first kind of observation is made by an employee who is not necessarily (or even usually) an auditor. This is an internal observation of an event or situation that may constitute a business risk or quality risk. This can be an observation of either an exceptional event or a routine activity.

Any organization whose processes are "in control" will have an administrative SOP, call it "Management Notification," that requires an employee to inform supervision of any event or situation that may impact the SISPQ of the product or constitute a business risk. FDA stipulates that it is the "person responsible for supervising" who must provide assurance of the SISPQ of the regulated product.[10] And supervisory personnel and management can only provide that assurance if they are notified of threats to the SISPQ of the product in a timely fashion. Management must be informed within a specified time frame so that appropriate action can be taken (Table 1.4).

The employee's observation will prompt one or more of the following responses from the manager. First, the manager may triage and dismiss the event as insignificant. Second, the

Table 1.4 Fields in typical Notice of Event form

1. Title of this event
2. Name of employee who observed this
3. Associated Quality Management System (QMS) tracking number(s)
4. Department where event was observed
5. Shift when event was observed
6. Date of discovery
7. Date of event occurrence (if known)
8. Employee involved in event
9. Other personnel involved
10. Symptom (problem type)
11. Attached files

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manager may call for immediate action to address the event that has been observed. Third, depending on the specifics of the Management Notification procedure, the manager may acknowledge receipt of the employee's observation. The employee may be required to submit the notification to management in writing; the manager may also be required to acknowledge receipt of the notification in writing. Fourth, the manager may escalate the notification further up the line. Fifth, management may organize an investigative team for the event, a team that is charged with discovering the root cause.[11]

The investigative team's report may lead to appointing a person responsible for preparing a CAPA plan (Table 1.5). In that case, management must also stipulate a due date for the CAPA. Insofar as the CAPA requires the revision of an operational SOP, the employee's observation initiates the chain of events that lead to the revision.

Table 1.5 Elements of CAPA

1. Analyze various sources of observations to identify existing and potential causes of quality problems.
2. Investigate the root cause of the quality problem.
3. Identify remediations to correct and prevent recurrence of the quality problem.
4. Verify that the CAPA is effective and does not create further problems.
5. Implement and record changes in methods and SOPs required by the CAPA.
6. Ensure that information related to the quality problems is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems.
7. Submit information on quality problems, as well as CAPAs, to management.
8. Document all activities under the CAPA.

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1.4.2 Quality audit observation

Any organization whose processes are "in control" will have a QA unit that is responsible for approving or rejecting the procedures, protocols, and specifications that impact the SISPQ of the product.[12] That unit must monitor the organization's compliance with these operational SOPs, which entails responsibility for quality audits and "reaudits of deficiencies."[13]

A quality auditor, at the conclusion of the audit, will document audit findings (i.e., observations) and report these to the manager of the unit that was audited. The manager will identify a responsible person to undertake or oversee whatever investigation and RCA is required. In the real world of limited resources, Lee Vanden Heuvel and Christine Robinson point out that an investigation must balance the costs of the effort against the expected benefit of identifying the root cause.[14]

Typically, an investigation includes the following main steps:

- Identify the problem;
- Evaluate the information, assess risk, take immediate remedial action;
- Investigate and assign responsibility;
- Analyze and document the root cause.[15]

FDA also stipulates that when an investigation is called for under 21 CFR 211.192 and is not conducted, "the written record shall include the reason that an investigation was found not to be necessary and the name of the responsible person making such a determination."[16] When the investigation is complete, the responsible person will then prepare a CAPA plan to address the observations, along the

lines suggested by the FDA and displayed in Table 1.5. The manager will also stipulate a due date for the CAPA.[17]

The quality audit observation will constitute the occasion for the revision of an operational SOP insofar as the remediation listed in the CAPA requires that revision. An example of this kind of observation, investigation, and CAPA would be an in-process quality observation of out of specification (OOS) levels of product variation. Management would order an investigation and then call for CAPA. The CAPA might propose that more specific directions were needed in the charging procedure (e.g., a more defined rate of addition of an ingredient) to minimize variation. These directions would be added to the operational SOP, either in the next routine biennial review or, more likely, by way of a PDP.[18]

As noted previously, a CAPA can call for all kinds of remediation for a given audit observation – business process redesign, risk mitigation, training intervention, organizational development initiatives, etc. Some intervention involves the revision of an operational SOP; for instance, business process redesign typically must be captured in a revised procedure. Other intervention does not; for instance, training interventions and leadership development initiatives usually do not require any change in an operational SOP. All intervention should contribute to continuous improvement of the GMP process.

This section has addressed the occasions for intervention that are a result of an internal observation – an observation of a discrepancy (or an opportunity for process improvement) that an employee escalates to supervision, or an observation made during a quality audit. In either case these may lead to the revision of an SOP. The next section examines occasions for remediation that are due to an external observation.

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1.5 Intervention due to external observation

There are three major occasions for intervention that may result from an external observation of a deviation and, therefore, may lead to the revision of an operational SOP. The first is an observation made by an investigator during a regulatory inspection.[19] The second is an observation associated with an AE. The third is an observation that accompanies a customer quality complaint.

1.5.1 Regulatory inspection

FDA has defined "an establishment inspection [as] a careful, critical, official examination of a facility to determine its compliance with laws administered by FDA."[20] More specifically, the inspection examines the organization's adherence to the concepts of sanitation and GMPs, seeks assurance that all reasonable precautions are being taken to ensure the SISPQ of finished products, and seeks to identify deficiencies as well as to obtain correction of those deficiencies. This inspection can be either comprehensive or directed. The comprehensive inspection covers everything in the organization subject to FDA jurisdiction to determine the organization's compliance status. The directed inspection covers specific areas to an assigned depth (*ibid.*).

In the case of a manufacturing site, this inspection will typically inspect the quality system and one of the other five systems of the FDA Quality Systems Approach: facilities and equipment, laboratory controls, production, packaging and labeling, and materials.[21] A regulatory inspection can include FDA personnel reviewing records of prior inspections,

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walking through the facility, examining current records, interviewing employees, etc.

When "deficiencies" are observed, they are reported to management before FDA personnel has left the facility. These Form 483 observations can later become part of an FDA Warning Letter to the management of the organization. At that point, if not earlier, the organization will begin to respond. The response typically includes management's call for an investigation of each deficiency observed during the inspection. Each investigation will include RCA, and tracking and trending of similar events or situations observed elsewhere or in prior inspections. CAPA will be developed and executed, all within a specified timeline. The remediation may require the revision of an operational SOP.

1.5.2 Adverse event

A second kind of observation is associated with an adverse event (AE). With respect to drugs, FDA has defined an AE as "any adverse event associated with the use of a drug in humans, whether or not considered drug related."[22]

Again with respect to drugs, a serious adverse event (SAE) is further defined by the FDA as:

> . . . any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization

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> may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (*ibid*)

Finally, an unexpected adverse event (UAE) is defined by the FDA as:

> . . . any adverse drug experience that is not listed in the current labeling for the regulated product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity.

The FDA explains further that:

> 'Unexpected,' as used in this definition, refers to an adverse drug experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product. (*ibid*)

FDA has provided analogous definitions of an AE for other regulated areas. Moreover, FDA requires "written procedures for the surveillance, receipt, evaluation, and reporting of post-marketing AEs."[23] FDA requires the investigation and reporting of AEs for many of the areas under its jurisdiction, as shown in Table 1.6. FDA encourages health care providers to report any AEs that the providers judge to be clinically significant.

Table 1.6 FDA predicate rules for adverse events

Regulated Area	Regulation
Animal drugs	21 CFR 514.80
Biologics	21 CFR 600.14, §600.80
Blood processing	21 CFR 606.171
GCP	21 CFR 310.305
GMP	21 CFR 211.198
GTP	21 CFR 1271.350(k)
Medical Devices	21 CFR 803.10

In a typical case, an AE report is initially recorded in the organization's drug safety information system within a specified period of time after receipt of the report (say one day). That record should include the name and title of the reporter (i.e., typically the health care provider), contact information for the reporter, the product in question including label information, and the patient's identifier.[24] A medical reviewer gives a preliminary judgment of the etiology, the "expectedness," and the severity of the AE, and provides a medical code for the event based on the *Medical Dictionary for Regulatory Activities* (MedDRA) or on an internal corporate code used to describe these events. The medical reviewer also determines whether the language describing the event is correct.

This is the point of initial triage.

If the event is judged as clearly not drug related, then the report is completed at this point. However, if it is not clear or is a SAE, then the event is escalated to the next level. Depending upon the preliminary assessment of severity, the case can be expedited. If so, information on this case is provided to FDA for "each adverse drug experience that is both serious and unexpected as soon as possible."[25]

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Subsequent investigation of an SAE includes the following two aspects:

1. Case specific – reviewing the demographics of the patient, dosage levels and length of exposure, other medications, and other medical conditions;
2. Tracking and trending similar events.

Then two other medical reviewers must independently review the case narratives and lab reports including the diagnosis, clinical course, therapeutic steps, and outcome of the event. They must also independently check the medical coding and confirm the case assessment. If the blinded assessments differ, they must be reconciled. Once reconciled, the case report is submitted to the company's Regulatory Affairs officer.

Remediation may be called for if the tracking and trending of similar events show a pattern and the trend reaches a predetermined threshold, or if the individual event is serious enough. In fact, the two factors that drive the decision to make a response are frequency and severity. If the event is a minor complaint (such as a rash) and also a frequent complaint, this may warrant a labeling change.[26] Remediation will also be considered for a more serious event, such as acute renal failure, that occurs at a low frequency. Insofar as remediation requires the revision of an operational SOP, the observation and reporting of an AE initiates the revision, similar to the case of the quality audit discussed previously.

1.5.3 Customer quality complaint

A third kind of observation takes the form of a complaint made by a customer routed to the organization's quality complaint unit (CQU). FDA has defined a customer quality complaint as "any written, electronic, or oral communication

that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a [product] after it is released for distribution."[27] Processing of complaints and maintaining complaint files is an FDA requirement for many of the areas under its jurisdiction, as displayed in Table 1.7.

Upon receiving a complaint, CQU conducts a triage whereby the complaint is classified according to type: routine complaint or urgent complaint. If the complaint is classified as routine, a response is prepared, routed via the QMS through the approval process and finalized, and the file is closed. No operational SOPs would be revised as a result of a routine complaint. If the complaint is classified as urgent, a record is opened in the QMS, the complaint is classified in terms of product quality complaint (PQC) criteria, and the complaint and supporting material are routed to the manufacturing site.

Management decides whether an investigation is required; if so, a responsible person is assigned the task of preparing an investigation plan, and a time schedule is developed. Preliminary tests are conducted, such as X-ray, visual inspection, and functional tests. If further investigation is

Table 1.7 FDA predicate rules for complaint files

Regulated Area	Regulation
GCP	21 CFR 310
GMP	21 CFR 211.198
GTP	21 CFR 864.3250; §1271.320
HAACP	21 CFR 123.8
Mammography	21 CFR 900.4
Medical Devices	21 CFR 814.9; §820.198
Medicated Feeds	21 CFR 225.115

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warranted, the complaint moves to the quality lab or other location where more tests are conducted and evaluations made. Finally, the findings and recommendations of the investigation are reported, routed through the approval process and finalized, and the file is closed. Insofar as the remediation following from the investigation includes the revision of an operational SOP, the customer quality complaint initiates the chain of events that lead to the revision.

1.6 Conclusion

This chapter has considered the occasions that lead to re-engineering of GMP processes and, under certain conditions, the revision of SOPs. Five groups of stakeholders in the sphere of FDA-regulated industry are identified. Particular kinds of observations that can occasion intervention tend to be associated with each of these stakeholders. While there is some overlap between them, escalated events tend to be associated with employees, internal audits with auditors, Form 483 observations with regulatory investigators, AEs with health care providers, and customer quality complaints with patients.

The observations initiate an investigation and remediation process that varies in emphasis but that has an underlying logic. An observation is typically escalated, triaged, and can become a record of interest in the organization's QMS. That record can become the basis of an investigation and RCA. It can also become part of a set of records of similar events that are tracked and trended, and investigated further. When the investigation is concluded, remediation can be proposed in the form of CAPA. The remediation is approved and enacted, and may include the revision of an SOP. Thus the initial

observation can constitute an occasion for the revision of the procedure. Moreover, a diligent approach to intervention can promote the continuous improvement of the GMP process.

From an organizational standpoint, it is clearly preferable to receive internal observations rather than external observations; it is preferable to conduct investigations, and to develop and enact remediation in response to observations by internal stakeholders, rather than waiting until the organization must respond to external stakeholders. Hence it is good strategy to encourage employees not only to bring suggestions for process improvement, but also to bring observations of events and situations that may constitute a business or quality risk, to the attention of supervision. It is also good strategy to have in place an administrative procedure that provides guidance in the timely, systematic, and appropriate management response to such observations.

1.7 Notes

1. For FDA 483 *Observation to Genzyme*. Available from: *www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM191991.pdf*
2. For FDA MAUDE AE Report on Genzyme Biosurgery's Synvisc injection. Available from: *www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/detail.cfm?mdrfoi__id=1099535*
3. See Natasha Singer (2010).
4. See David C. Peterson (2006).
5. For the requirement of "written procedures," see 21 CFR 211.100. For the requirement that they "shall be followed," see 21 CFR 211.22, ∫211.80, etc. On the

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regulatory side, see Denise Queffelec and David Peterson (2008):

> Failure to follow established SOPs is one of the most frequently cited violations in FDA 483s and warning letters. The frequency of SOP-related violations points to the need for all regulated companies to review their SOPs, their methods for distributing compliant SOP training curricula, their methods of validating receipt and testing for comprehension of the materials, and their documentation of SOP training activities.

6. 21 CFR 10.115. As Steven Weil (2004) has put it:

> A *predicate rule* is an FDA regulation such as Good Laboratory Practice (GLP) or Current Good Manufacturing Practice (cGMP). Predicate rules mandate and define: What records must be maintained; The content of the records; Whether signatures are required; How long records must be maintained.

7. 21 CFR 211.100. Of course the changes may be improvements, or the opposite (i.e., procedure "churn").
8. This has been recognized by the International Conference on Harmonization (ICH) (2008) in its call for a system for implementing CAPAs resulting from the investigation of a wide range of observations, including "complaints, product rejections, non-conformances, recalls, deviations, audits, regulatory inspections and findings, and trends from process performance and product quality monitoring [. . .] throughout the product life-cycle."

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For the predicate rules regarding GMP processes, see 21 CFR 211.192, Production record review:

> Any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated. The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. A written record of the investigation shall be made and shall include the conclusions and follow-up.

We take "unexplained discrepancy" to imply an observation, "other batches" to imply tracking and trending, and "conclusions and follow-up" to imply remediation.

9. 21 CFR 211.100.
10. 21 CFR 211.25(b).
11. See also 21 CFR 211.192 "Production record review."
12. This is explicit in 21 CFR 211.22; it is more implicit in 21 CFR 1271.160. Again, all these controlled documents are referred to herein as "procedures" or "SOPs."
13. 21 CFR 1271.160 (b)(3). See also Tim Fields (2008).
14. See Lee Vanden Heuvel and Christine Robinson (2005). Their Figure 1 provides a very useful overview of the tradeoff between level of effort versus return in a RCA. The ICH (2009) has stated that "The level of effort, formality, and documentation of the investigation should be commensurate with the level of risk." Jerome Spear (2002) discusses setting priorities in such a real world.
15. See also James Sandler (2008); Emma Barsky and Len Grunbaum (2008); and Doug Bartholomew (2006). For a discussion of the problems of "silo thinking," "finger

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pointing," and "jumping to conclusions" that bedevil real-world investigations, see Chris Eckert (2008).

16. See 21 CFR 211.198(b)(3), ∫106.100(k)(2), ∫820.198(b), ∫1271.370(b), etc.
17. See, for instance, 21 CFR 820.100 "Corrective and preventive action," also ∫806.10 "Reports of Corrections."
18. As the ICH (2008) has pointed out, "CAPA methodology should result in product and process improvements and enhanced product and process understanding." This highlights the role of remediation in continuous improvement.
19. A regulatory inspection could be conducted by the EPA (focusing on emissions and waste), the DEA (controlled substances), etc. Chapter 6 discusses the regulatory overlap between these various agencies. This present chapter limits the discussion to the FDA.
20. See the FDA *Investigations Operations Manual* (2008) Sect. 5.1.2, "Inspectional Approach," and Sect. 5.51 "Drug Inspections."
21. See the FDA guidance *Quality Systems Approach to Pharmaceutical cGMP Regulations* (2006); also Karyn Campbell (2008).
22. 21 CFR 310.305(b) "Records and Reports."
23. 21 CFR 310.305(a) "Records and Reports."
24. See also Robert Nelson, *et al.* (2002). Note that the reporter could be anyone, including the patient. Most organizations require that an employee report within one business day if a person complains about some physical problem or symptom and mentions they are taking one of the organization's products.
25. 21 CFR 310.305(c)(1), "Post-marketing 15-day 'Alert reports'." Many organizations provide these reports in seven days. In addition, AEs relating to a regulated

product are reviewed every six months for each regulated product and an updated report is filed with the FDA.

26. Remediation may involve a "Dear Investigator Letter" (DIL) if it is observed during a clinical trial. A DIL is prepared if an AE occurs during a clinical trial and is confirmed or reasonably certain to be related to the regulated product. Incidentally, the term CAPA is rarely used in clinical studies. If this is a post-marketing trial or observation, then changes to the labeling may be considered.
27. 21 CFR 820.3(b), "Definitions."

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2

Investigations, root cause analyses and CAPAs

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Abstract: This chapter considers the organizational response to observations, particularly those occurring in manufacturing and quality lab areas. Observations are either triaged or they are escalated. A number of observations that will likely result in escalation are listed, as well as a number that will likely be triaged because they are non-GMP issues. Next, this chapter addresses the process of investigation and root cause analysis (RCA). Finally, it discusses the corrective action and preventive action (CAPA) that are the outcome of the investigation.

Key words: corrective action, deviation investigation, escalation, human error, Ishikawa diagram, Notice of Event, preventive action, program logic model, remediation, root cause, triage.

2.1 Triage and escalation

Resources are limited – resources such as staff who are experienced in conducting investigations, resources such as

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time to conduct investigations. It is necessary to ensure that those scarce resources are being expended on critical issues. A non-GMP issue such as a burned out ceiling light bulb is usually less critical than a GMP issue such as failure to follow a standard operating procedure (SOP). Triage is the process of ranking events or things in terms of importance or priority; resources are allocated accordingly. For our purposes, triage is binary – some observations will be set aside, while others will be escalated further.

In the manufacturing and lab areas, an observation will typically result in a Notice of Event (NoE), whereby employees notify management that something has been observed, an exceptional event has occurred. Should the observation be triaged, it will be set aside, it will remain at the level of "NoE Only." However, if the observation and associated NoE is escalated, then an investigation may occur.

The decision to escalate is not a trivial one. As Margaret Hambleton has expressed it:

> A formal, well-documented RCA should be conducted when you are investigating a significant compliance failure. It should be used in those situations where reoccurrence would have a significant impact. You typically would not use an RCA for simple mistakes, inadvertent slips, or one-time events. You would consider using an RCA when those simple mistakes turn into a trend.[1]

Table 2.1 shows some of the kinds of observations in the manufacturing area that will likely be escalated.

Table 2.2 shows some of the kinds of observations in the quality labs that will likely be escalated.

There are a number of observations that will most likely

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Table 2.1 Illustrative production observations that will be escalated

1. Deviation from an SOP
2. Foreign matter
3. Processing issues that result in segregating and destruction of product
4. Non-adherence to specified time limits for a processing step
5. Temperature, humidity, and/or pressure excursions during batch processing
6. Product attribute defect issues
7. Raw materials found damaged during inspection
8. Contaminated product
9. Out-of-calibration results for GxP instruments
10. Use of non-calibrated GMP equipment
11. Use of non-qualified GMP equipment
12. Missing data
13. Rejected materials not properly identified and controlled
14. Use of an incorrect form to record GMP activity

Table 2.2 Illustrative lab observations that will be escalated

1. Deviation from an SOP
2. Out-of-Spec (OOS) test results
3. Microbiological cleaning failures
4. Incorrectly labeled samples
5. Error in stability samples for testing
6. Identification of an adverse stability trend
7. Use of non-calibrated GMP equipment
8. Use of non-qualified GMP equipment
9. Missing data
10. Use of an incorrect form to record GMP activity

be triaged, typically because they are not GMP issues, as displayed in Table 2.3.

In any case, the observations (events) that are escalated will

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Table 2.3 Illustrative observations that will be triaged

1. Minor documentation errors that are addressed in the record
2. Typographical errors (e.g. misspelled words, grammatical errors, punctuation errors)
3. Missed periodic maintenance, out of calibration status of non-GMP equipment
4. Equipment challenge failures that occur during set-up
5. Shutdown of the redundant utility system
6. Utility shutdown that does not disrupt operations
7. Routine service calls
8. Materials spilled during weighing, measuring, or dispensing operations

lead to investigations and root cause analyses.

This section has discussed the kinds of observations that are likely to be escalated, and those that are likely to be triaged. The next section will consider the process of investigation that follows from an escalation.

2.2 The process of investigation

Faced with a problem (call it P) that is referenced in a NoE – a manufacturing deviation or out-of-spec lab result, say – the organization will conduct an investigation to find the root cause.

Management assigns an employee to lead the investigation, typically a subject matter expert (SME), and establishes the due date for the completion of the investigation report. The lead investigator will review the NoE and also review related observations (events), trend data, training records, etc. Of particular interest is determining whether this deviation is a recurrence, which means that earlier remediations have

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failed. In such a case, the prior corrective action and preventive action (CAPA) must be reconsidered to determine why it failed.

It is usually recommended that a team be assembled by the project lead, since this permits triangulation in assessing the deviation and its causes. This also improves the likelihood that the effects of personal biases in assigning causes will be lessened.

Many times the investigation of a deviation involves a number of departments. This requires a cross-functional investigation involving employees from various departments to assess the deviation. The participants should consist of SMEs from departments that have been impacted by the deviation, as well as personnel from Quality Assurance (QA).

The investigation will identify a number of elements of the manufacturing or quality lab system, call them E_n, where the variation in E_i causes variation (deviation) in P. Consider the following Ishikawa diagram.[2] Six major elements are included (Figure 2.1).

Elements that are identified as part of E_n – that is, potential causes of the deviation – can be considered as elements of the FDA Quality Systems Approach, including equipment, production, quality, materials, laboratories, packaging, etc.[3] Consider the Ishikawa diagram displayed in Figure 2.2. Each of these elements has its own constituents. The investigation

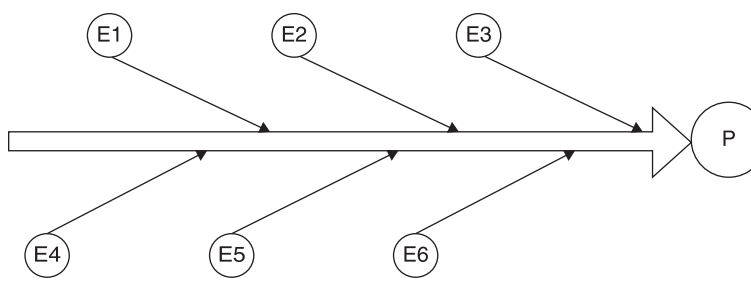

Figure 2.1 Template of Ishikawa diagram

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proceeds by eliminating the various elements and constituents of the system that might have been the cause of the deviation. Each of the elements and constituents is reviewed in turn (Figures 2.2 and 2.3).

The disaggregation of a major element, say equipment, into its constituents is illustrated in Figure 2.3. For example, what is the ease of operation of this piece of equipment? Was the equipment maintained (or not)? Was it calibrated? Was this piece of equipment appropriate to the tasks? Were there adequate units of equipment?

By a process of elimination, elements and constituents are considered and eliminated once it is determined that each could not have been the root cause of the deviation, until

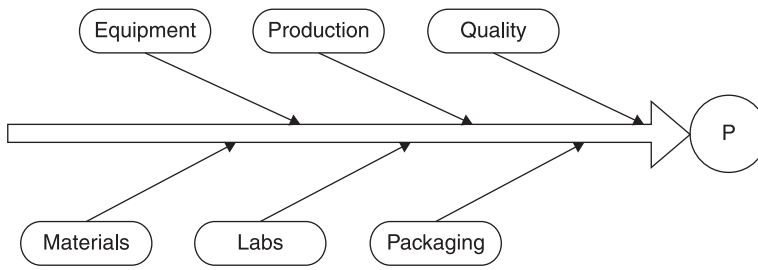

Figure 2.2 All candidates for root cause

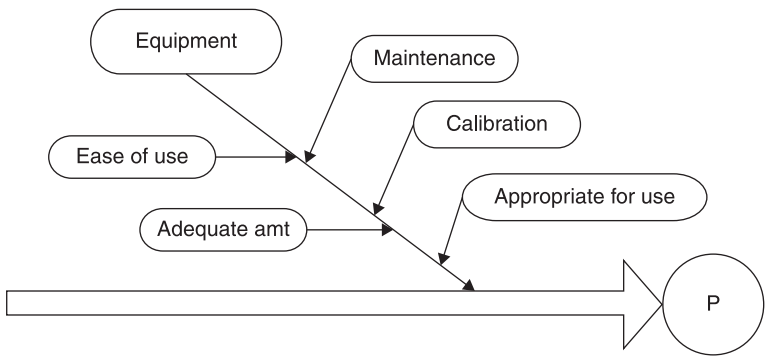

Figure 2.3 Disaggregation of a major element

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only one remains. That remaining element or constituent is labeled the "root cause," or, sometimes, the "probable root cause."[4]

It is important to consider the entire set of elements that are candidates for the root cause. Wald and Shojania point out that "a credible RCA considers root causes in all categories before rejecting a factor or category of factors as non-contributory."[5]

Investigators are sometimes prone to identify an individual employee as the "responsible party" for a deviation. As the noted authority on accident investigation, James Reason explains this tendency, "blaming individuals is emotionally more satisfying than targeting institutions."[6]

In his analysis of models of human error, Reason distinguishes between the "person approach" and the "system approach." Human error can be error in the here and now, or it can be error inadvertently incorporated at some time in the past into human products, such as complex health care systems, laboratory systems, or manufacturing systems. Thus Reason distinguishes "active failures" associating human error with individual persons and "latent conditions" associating human error within a system.[7] The latent conditions prove more potent in causing deviations than do the active failures (Table 2.4).

The RCA process has two main phases. In the first phase, data must be collected allowing a timeline to be sketched that includes: (a) that which precedes the event; (b) the deviation (event) itself; and (c) that which follows the event.

In the second phase, data are analyzed to allow the causes of the event to be identified, in terms of both the active failures and the latent conditions. An example of an active failure would be an employee who fails to follow an SOP; a latent condition would be a poorly-written SOP.

Table 2.4 Reason's models of human error

Locus of error	Person	System
Focus of analysis	Active failures – Errors of individuals	Latent conditions – Conditions under which individuals work
Root cause	■ Forgetfulness ■ Inattention ■ Poor motivation ■ Carelessness, negligence and recklessness	■ Errors show recurrent patterns ■ Same set of circumstances can provoke similar errors, regardless of the people involved
Remediation	■ Poster campaigns that appeal to people's sense of fear ■ Writing another procedure ■ Disciplinary measures ■ Threat of litigation ■ Retraining ■ Naming, blaming, and shaming	Seek out and remove the error provoking properties within the system at large

As the various elements are eliminated, the set of candidates for "root cause" decreases. Suppose the only elements remaining are materials and packaging and labeling (Figure 2.4).

The same approach can be applied to the packaging and labeling element. The packaging and labeling materials had been appropriately inspected, recorded, stored, etc. by procedure (or not). Labels had been issued according to procedure (or not). The other constituents of the packaging element include the packaging and labeling operations themselves, the tamper-evident packaging, the inspection of finished packaged and labeled products, and the expiration dating (Figure 2.5).

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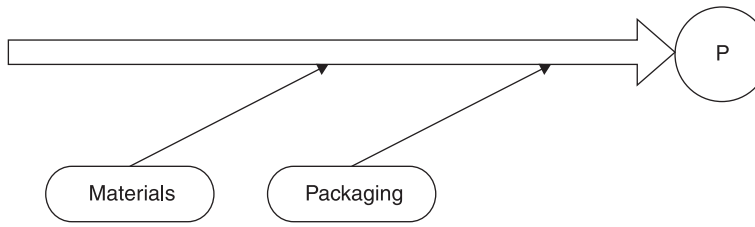

Figure 2.4 Remaining candidates for root cause

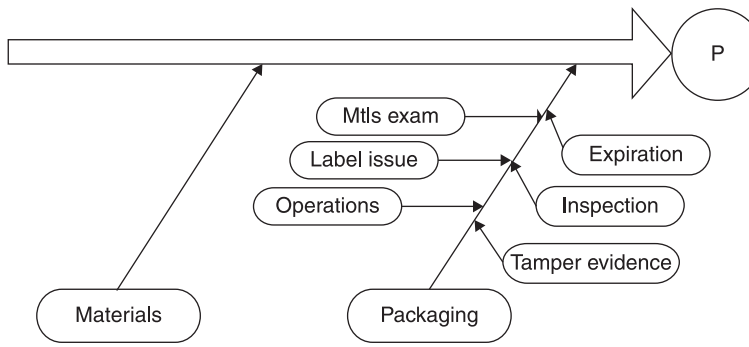

Figure 2.5 Constituent elements of packaging and labeling

Each constituent element is considered and eliminated from consideration when it is determined that it could not have been the root cause of the deviation.

When the investigation is complete, and a root cause or probable root cause has been identified, the project lead will prepare a Final Investigation Report (FIR) to submit to management for review and possible approval. The report should include the sections displayed in Table 2.5.

As an executive summary of the FIR, the Investigation Summary includes the sections displayed in Table 2.6.

Management will review the FIR, and decide on the appropriate CAPA, including a reconsideration of previous CAPAs as necessary.

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Table 2.5 Format of final investigation report

1. Investigating area
2. Lead investigator
3. Investigation Summary (see Table 2.6 below)
4. Impact Assessment
5. Description of Deviation
6. Investigation Conclusions, including root cause
7. Recommended material disposition (if applicable)
8. Disposition Justification (if applicable)
9. Proposed Corrective Action/Preventative Action

Table 2.6 Format of investigation summary

1. A chronology of events, date of occurrence, etc.
2. Immediate actions taken
3. Areas evaluated
4. Supporting documentation
5. Rationale for the exclusion of potential root causes
6. Review of related incidents, review of historical/trend data, and/or whether it is a repeat occurrence

This section has discussed the process of investigation that follows from the observation of a deviation. The next section will consider the process of CAPA.

2.3 The process of CAPA

Once the investigation is completed and the root cause identified, remediation can take place. Remediation takes the form of corrective actions, to remedy the situation in the here and now, and preventive actions, to ensure that the problem does not recur.

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In the case of a CAPA project, management appoints an employee responsible for executing the CAPA, typically a SME, and also stipulates the due date for the completion of the CAPA project.

The project lead will first review the documentation associated with the just completed investigation as well as the documentation of related CAPAs.

Second, the project lead will develop a template that will facilitate the comparison of the currently existing program – the object of the investigation, the RCA, and the CAPA – with the desired (revised) program. The comparison can be facilitated by casting the program and the proposed preventive action into the framework of a program logic model.[8]

Suppose that an observation was made for a cleaning and sanitizing program. The levels of bioburden in controlled areas was outside acceptable limits. The investigation found that the specified sanitizing solution was too weak. The proposed remediation was to increase the concentration of the solution. The elements of the CAPA are displayed in Table 2.7.

The program for cleaning and sanitizing of controlled areas illustrates the role of CAPA (Figure 2.6). Under *Inputs* are included the input measures such as the cleanliness of controlled areas as well as the determination of bioburden of controlled areas. Other inputs include the various cleaning and sanitizing materials (e.g., cleaning agents, sanitizing agents, isopropyl alcohol, mops and mop buckets, cleaning carts, etc.) The *Input Criteria* for these measures are visually determined soiling of surfaces in the controlled area, and environmental monitoring (EM) data indicating unacceptably high levels of microbial contaminants. These criteria identify the "gap," mentioned earlier, that is the observation that triggers intervention and remediation. The input criteria also include the various approvals of the listed cleaning and sanitizing materials.

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Table 2.7 Elements of the program logic model

- **Input variables**: a set of qualitative or quantitative variables that describe the initial state of the program (e.g., level of cleanliness of controlled areas; level of bioburden of controlled areas, etc.).
- **Program preconditions**: relatively invariant program elements without which the program could not exist (e.g., cleaning and sanitizing budget, GMP facilities, etc.).
- **Input criteria**: a set of ranges or values for the input variables and preconditions that establish cutoff points for program functioning.
- **Program process**: a set of program elements that act upon the variables and transform the initial program states into terminal program states. These process elements include the corrective actions and the preventive actions.
- **Output variables**: the set of variables descriptive of intended program change as well as a record of the terminal state of the program.
- **Program objectives**: (formally output criteria), which represent the standards against which program performance is to be compared.

The *Preconditions* for the cleaning and sanitizing program include the cleaning and sanitizing budget, GMP facilities, personnel, availability of the requisite time, place, and materials (e.g., sanitizing agent, yarn mops, personal protective equipment), etc.

Under *Process*, cleaning activities include the removal of debris and soiling to decrease the bioburden by removing organic material, as well as inorganic material that harbors organic material. The cleaning activities precede sanitizing procedures. Sanitizing activities include preparing the sanitizing agent, using the double bucket method, using the appropriate personal protective equipment, etc. Process criteria include the specific solution of the cleaning agent, the specific solution of the sanitizing agent, appropriate use of personal protective equipment, etc.

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	Inputs ⇒	Process ⇒	Outputs
Variables	• Level of cleanliness • Level of bioburden • Personnel measures (reflected in ITPs) • Various cleaning and sanitizing materials	• Preparation of solutions • Cleaning activities • Sanitizing activities	(Same as input variables)
Preconditions	Management support; Cleaning and sanitizing budget, staff qualifications; facilities, etc (Same throughout program cycle by definition)		
Criteria	(One for each input variable and precondition above) • Level of cleanliness is visually determined • Level of bioburden is environmentally monitored • Staff are trained on cGMPs and relevant SOPs • Approvals of listed cleaning and sanitizing materials	(One for each of the process variables) • CAPA: Increase the concentration of the sanitizing solution	(These define the objectives of the program in terms of the variables) • Level of cleanliness is visually determined • Level of bioburden is environmentally monitored

Figure 2.6 **Program logic model of cleaning and sanitizing program**

Finally, under *Outputs*, the criteria include the visually determined cleanliness of the controlled area and EM data that now fall within acceptable limits.

Once the program has been documented in a program logic model, planned changes can be examined in a straightforward manner.[9] The CAPA, in this illustrative case, amounts to an increase in the concentration of the sanitizing solution. All the other *Variables, Preconditions*, and *Criteria* would remain the same, so the effect of the planned change could be observed. Should the output not change, then the CAPA has failed. Moreover, the fully developed program logic model highlights the possibility of unintended consequences of the CAPA intervention.

Insofar as the CAPA requires the revision of an operational SOP, the original observation initiates the chain of events that lead to the revision.

2.4 Conclusion

This chapter has considered the activities that are triggered by the escalation of a deviation. These activities include an investigation, a RCA, and corrective action designed to remedy the problem in the here and now, and preventive action designed to prevent the recurrence of the problem. These activities may lead to the revision of one or more SOPs. The following chapter will discuss these implications.

2.5 Notes

1. See Margaret Hambleton (2005).
2. See Gary McLean (2005); see also Kaoru Ishikawa (1990).
3. See FDA *Guidance for Industry* (2006).
4. See Julie D. Honsa and D.A. Mcintyre (2003). "Sometimes the actual cause cannot be proven but only speculated by the process of elimination."
5. See Heidi Wald and Kaveh G. Shojania (2001).
6. See James Reason (2000).
7. See James Reason (2004). Reason goes on to say:

> latent conditions possess two important properties: first, their effects are usually longer lasting than those created by active failures; and second, they are present within the system prior to an adverse event and can be detected and repaired before they cause harm.

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8. See Leslie J. Cooksy, Paige Gill, and P.A. Kelly (2001); Nancy L. Porteous, Barbara J. Sheldrick, and Paula J. Stewart (2002); Robert L. Schalock and Gordon S. Bonham (2003); and Knowlton Johnson, Carol Hays, Hayden Center, and Charlotte Daley (2004).
9. See Gordon Welty (1970).

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3

The role of critical review in the revision of procedures

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Abstract: This chapter addresses changes to processes and the revision of standard operating procedures (SOPs). Emphasis is put on the necessity of SOP revisions. An illustrative problem is presented – an example of a laboratory weighing procedure and the development of a corrective action and preventive action (CAPA) project. Procedural changes in the example are evaluated and reviewed for regulatory compliance. The management of change depending upon risk assessment is considered.

Key words: calibration, CAPA plan, change management, complexity, critical review, criticality, real-world challenge, risk assessment.

3.1 Introduction

Given the ubiquitous changes in technology, procedures must be appropriately revised. The key word here is "appropriate." Revisions – the "versioning up" – of a standard operating procedure (SOP) that adds value to a procedure can contribute to best practices. Revisions that

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do not add value are wasteful, and from a regulatory standpoint suggest that a process is not in control. In order to ensure that the revision is appropriate, the SOP should be subjected to critical review. Newly written procedures can also be subjected to critical review.

Approaches to the critical review of procedures vary in terms of increasing credibility of the review findings. It is a prerogative of management to weigh the benefits of increasing credibility against the costs of increasing rigor of the approach. This cost/benefit analysis must be informed by a determination of the degree of change that is involved in the revision, as well as a risk assessment of the change.

After examining the critical review of SOPs, this chapter will consider how the management of change depends upon risk assessment. It has three components: risk identification, risk analysis, and risk evaluation. The criticality and complexity of the process tends to increase the level of risk. And the appropriate level of critical review and effort supporting implementation of change is directly related to the criticality and complexity of the process.

Following the discussion of risk, an illustrative problem is presented. Over time, the variability of the potency of an active pharmaceutical ingredient (API) was seen to increase. This is a complex problem, implicating the weighing facility and instruments for the analytical standard, as well as the associated weighing procedure and calibration procedure. It is also clearly a critical problem, as the potency of the API impacts the quality attributes of the product.

A CAPA plan is developed and implemented to remediate the facility and instruments; this leads to revisions to the relevant SOPs. It is necessary to review critically the adequacy of these revised procedures. The CAPAs are tested, and the results lead to informed decision making about the changes as well as mitigation of the original problem.

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This chapter concludes by considering the place that the critical review of procedures holds in a value-adding approach to program design and management.

3.2 Overview of critical review of SOPs

An SOP is a "process control;" it controls the execution of a process. The SOP can address several kinds of process – a person-to-machine process, a person-to-paper process, a person-to-person process, or a combination of the three processes.[1]

The SOP is a controlled document, meaning it is subject to change control. Any proposed changes to this document (and the real-world process it reflects) must be processed and approved according to the applicable change control process, as stated in the organization's change control procedure.[2] The proposed change request must indicate any impact the changes will have on process, material, product, regulatory filing, other good manufacturing practice (GMP) sites, etc. The request must identify activities, responsible parties, time frames and due dates, and deliverables comprising the proposed changes.

Given the constancy of technological change – as well as the frequency of non-conformances (unplanned deviations), associated investigations, and CAPAs – procedures must be revised. Revisions should be value-adding activities, but often are not. When the revision does add value, it can contribute to best practices in development or manufacturing. When it does not add value, it is sometimes called "procedure churn;" other times it is called "word-smithing." From a business standpoint, procedure churn is wasteful, hence uneconomical. From a regulatory standpoint it also suggests

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that a process is not in control. In order to ensure that the revision adds value (i.e., adds content that is needed and no more), the SOP should be critically reviewed.

The critical review of an SOP ensures that the process addressed in the procedure, as written and executed, will attain the outcome the organization wants. The critical review of a revised procedure ensures that the proposed changes will add value to the process. Addressing "validation of both the process and process controls," FDA defines validation as follows: "Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics."[3] Various approaches to validation can then be ranked in terms of the "degree of assurance," or credibility of the resulting evidence. The same is the case for the critical review of procedures.

Take a drafted SOP, whether a newly written procedure or a revision of a current one. Critical review of the SOP consists of one or more of the following approaches, listed in terms of increasing credibility of the resulting evidence:

- management review during the SOP approval process;
- expert review by subject matter experts (SMEs) or others;
- step-by-step real-world challenge;
- experimental design study.

Management review is the vetting of the procedure as it goes through the several iterations of the document change process. The management of each department that will be impacted by the revisions has the opportunity to review the draft, suggest changes, and sign off on the document. Everything in management review will routinely be captured in the document change process.

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Management review provides the lowest degree of assurance of the resulting evidence among the several approaches. This is in good part due to the organizational role of management review in the document change process. The manager of each department, or the designee, looks for the potential impact of the revision on that department. The manager also looks for departmental responsibilities and responsible persons. Beyond those issues, there is little interest in the critical review of the procedure.

In the case of *expert review*, the SMEs will review the draft for both positive and negative elements. On the positive side, they will look for best practices, value-adding steps, flexibility in light of changing demands, scalability in light of changing output targets, etc. On the negative side, they will look for bottlenecks in the process, duplication of effort, unnecessary tasks, non-value-adding steps, role ambiguities (i.e., several positions responsible for a task, or no one responsible for a task), etc. It is important to document all the points raised by the experts in their review.

Expert review provides a higher degree of assurance than management review, because it is a compilation of expert opinion, and it is focused on the technical content of the procedure. The International Organization for Standardization (ISO) has stipulated that validation evidence should be "objective."[4] The same is the case for the critical review of procedures. The opinions of SMEs, while clearly not the simple prejudices of lay persons, are also not clearly "objective."

The *real-world challenge* tests the procedure's applicability by challenging it step-by-step on the floor or lab bench. This involves selecting one (or more) seasoned employee(s) within the scope of the draft procedure – not necessarily a SME – and comparing the steps as drafted in the procedure with the employee's activities. It is important to ascertain if they align. It is equally important to consider evidence of resistance,

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repetition, and human factor problems like task difficulty. Once again, it is critical to document everything in the challenge.

This challenge provides a greater degree of assurance about the resulting evidence because it is an objective test of the procedure's applicability. However, it does not control a number of internal and external threats to validity. Internal threats to validity, such as history effects or maturation effects, may provide plausible alternative explanations of the resulting evidence.[5]

The revised procedure may "look" better than the current procedure, but it may appear so because this particular operator, at this time and place, performs better because she or he got the prized place in the company parking lot that morning. External threats to validity (and the associated threats to "transferability"), such as expectancy effects, also called Rosenthal effects, may limit the generalizability of the resulting evidence. The operator may perform better because the vice-president of technical operations has inadvertently communicated her expectations for the real-world challenge.[6]

Nonetheless, it provides more credible findings for the decision either to proceed with versioning up the SOP, or to introduce further revisions in the procedure.

Suppose that management cannot make a decision about the applicable standard, say the concentration of the sanitizing solution, by means of management review, peer review, or the real-world challenge. Conducting a *study based on an experimental design* is an option that management can consider. Such a study will control for internal and external threats to validity, thereby providing credible findings for the requisite decision.

The proposed study is a randomized design examining the efficacy of several levels of concentration of the solution as applied to randomly selected sites in the facility.[7]

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The model for this randomized block design is:

$$Y_{i,j} = \alpha + \beta_1 x_i + \beta_2 x_j + \varepsilon$$

where:

$Y_{i,j}$ is observation *i, j*;
α is the mean;
β_1 is the effect of the primary factor, the levels of concentration of the sanitizing solution (*i* = level 1; level 2, . . . level mean;
β_2 is the effect of other program factors;
ε is the random error term.

The observations will be the environmental monitoring data from the sampled sites. The primary factor, the levels of concentration of the sanitizing solution, will range from the level 1 to the level n concentration.

Immediately following sanitizing activities by the members of the sanitizing and cleaning unit, EM data will be collected and appropriately recorded.

The study hypothesis addresses the effect on bioburden of the levels of concentration of the sanitizing solution. The higher the level of concentration, the greater the reduction of the bioburden. Given the analysis of variance (ANOVA) and the F-distribution, if $F_0 > F_a$ we may conclude that the factor values are different for a given significance level *a* and the null hypothesis is to be rejected. Such findings will provide very credible inputs for the requisite management decision about the revision of the procedure.

These approaches to critical review are ranked in terms of increasing credibility of the results. When selecting between them, management must weigh costs against benefits, comparing the costs of increasing rigor to the benefits of increasing credibility of the findings.[8] Typically, the approach

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to critical review of procedures that is selected will be part of a more general CAPA project.

This section has discussed how revisions to SOPs should be critically reviewed in the same manner as changes to processes such as manufacturing processes, cleaning processes, analytical methods, etc. As mentioned previously, risk assessment should be included in the weighing of costs and benefits.[9] An SOP that is associated with a process or component of greater complexity and criticality will have more stringent requirements, and will require a more critical approach to the review of the procedure.

3.3 Risk assessment and critical review

The critical review of a new or revised procedure should be guided by the following three fundamental questions, all elements of risk assessment:

1. What might go wrong with the associated process? Answering this question involves *risk identification*.
2. What is the likelihood that this will go wrong? A *risk analysis* addresses this second question.
3. What are the consequences? How severe are they if this goes wrong? *Risk evaluation* provides an answer to this question.[10]

The first of these three questions raises the issue of the *complexity* of the associated process. Definitions of complexity include the following:

- *Interconnectedness*: the organization and interaction of system components;

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- *Time-variance*: the repeatability of the system's response to control stimuli;
- *Information content*: the amount of information needed to deal with the system from a particular perspective such as creation, use, or maintenance.[11]

Test categorization, which measures the complexity of laboratory tests covered by the Clinical Laboratory Improvement Amendment (CLIA), provides one illustration of the measurement of complexity.[12] Using the seven criteria listed in Table 3.1, a laboratory test is graded for level of complexity by assigning scores of 1, 2, or 3 within each of the criteria.

A score of "1" indicates the lowest level of complexity, and a score of "3" indicates the highest level. These scores are then totaled. Laboratory tests receiving scores of 12 or less are categorized as moderate complexity, while those receiving scores above 12 are categorized as high complexity. An analogous approach could be used to measure the complexity of another process.

The higher the complexity, the more the likelihood that something will go wrong in the process. *Risk identification*

Table 3.1 **Measuring the complexity of lab tests**

Criteria Score =	1	2	3
1. Knowledge			
2. Training and experience			
3. Reagents and materials preparation			
4. Characteristics of operational steps			
5. Calibration, quality control, and proficiency testing materials			
6. Test system troubleshooting and equipment maintenance			
7. Interpretation and judgment			

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becomes more difficult as the process becomes more complex. This is because increasing complexity increases uncertainty about a process, "uncertainty due to combination of incomplete knowledge about a process and its expected or unexpected variability." Since risk identification "provides the basis for further steps in the quality risk management process,"[13] increased complexity of a process, as well as the associated detectability of the various hazards, makes the *risk analysis* – the second of the three questions, involving an estimation of risk associated with an identified hazard – more difficult.

The third question raises the issue of the *criticality* of the process. The Criticality Task Team of the ISPE Product Quality Life-cycle Implementation (PQLI) initiative has provided the following comments on the concept of criticality and its measurement.[14] A component of a system is categorized as potentially critical, in contrast to some other component that is categorized as non-critical, in terms of the severity and probability of risk that component poses to the safety, efficacy, and quality of the product, and harm to the patient. The relative level or degree of risk a component poses is assessed relative to the probability of occurrence, detectability, and potential harm to the product or the patient.[15]

The more critical the process or component, the more severe the consequences should something go wrong. In brief, a procedure for supplier quality control (QC) is more complex than an SOP for signature cards; a procedure that provides guidance to a process that "touches the product" is more critical than an SOP for cartonizing a secondary package. As the International Conference on Harmonisation (ICH) has expressed it: "the level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk."[16] Thus, the

Table 3.2 Complexity and criticality of process

		Criticality		
		Low	Med	High
Complexity	Low	A		
	Med		B	
	High			C

review must take into account the dimensions of complexity and criticality of the associated process.

Table 3.2 displays the dimensions of complexity and criticality.

When the Complexity × Criticality is Low/Low (Scenario A in Table 3.2), the first approach (the management review of the new or revised procedure) may be appropriate. A procedure for weight checks of cartons might be an illustration of Scenario A. When the Complexity × Criticality is Med/Med (Scenario B in Table 3.2), the second approach to the critical review of the new or revised procedure, expert inputs, may be appropriate. The acquisition of a new model of a lab balance, and the issue of the revisions to the procedure for weighing this purchase requires, might be an illustration requiring more than management review. Finally, when the Complexity × Criticality is High/High (Scenario C in Table 3.2), the critical review of the revised procedure may necessitate a step-by-step challenge. The planning of a new central weigh facility, and the procedures that will be necessary in that facility, might be an illustration requiring more than SME inputs.

This section has discussed how risk assessment is an important component of the management of change. The level of critical review and appropriate work supporting implementation of the change is directly related to the

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criticality and complexity of the process. The next section presents an illustrative problem that requires an investigation, leading to the development of a CAPA plan that calls for changes in process as well as revision of analytical laboratory procedures.

3.4 Investigating a complex × critical problem

FDA-regulated industry must have a written procedure that defines "events of concern," which include actual departures from established, approved SOPs, material specifications or manufacturing orders, etc. as well as potential departures (e.g., in the form of trends observed in a product-monitoring system). Regulated industry must also have a procedure for the conduct of investigations of such departures, insofar as they actually or potentially impact the quality attributes of the product.[17]

These procedures were followed regarding the illustrative problem presented in the following example.

3.4.1 An illustrative problem

A QC staff member reported an increasing variability in the determination of potency of the active drug of a pharmaceutical product, a commercially available FDA-approved tablet. The variability of data on product potency did not fail specifications and was not sufficient to cause risk to patients taking the drug. However, the variability was not consistent with manufacturing data from similar products and/or processes in the same facility. Tracking and trending suggested the increasing variability should be dealt

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with, because it potentially impacted the quality attributes of the product. Thus the criticality of the problem was recognized from the start.

A deviation investigation team was formed including responsible manufacturing, quality assurance, and laboratory management and key personnel, and a project manager was designated. This team initiated an investigation to address the increase in data variability, beginning with a comprehensive review of the product manufacturing process. Their review focused on activities specifically influencing drug potency. Activities reviewed included active drug weighing and dispensing, active ingredient charging steps in the manufacturing process, sources of process variation, possible drug loss in processing, sampling of tablets for potency testing, and analytical testing including all associated procedures. The range of areas and activities included in the investigation highlight the complexity of the problem.

A more specialized review team was formed in the analytical area. This review team comprised the analytical department manager, SMEs, laboratory analysts, and associated personnel. This team reviewed all activities associated with the drug potency assay, including standard preparation, incoming sampling control, sample preparation, high performance liquid chromatography (HPLC) instrument control and operation, calculations, and other associated activities. The accuracy of weighing the analytical standard for the API was suspected as a potential contributing factor to the increasing variation in drug potency. Variability in weighing the analytical standard would in turn cause variation in the potency determination of the tablet product.

As part of its investigation (or perhaps "sub-investigation"), this team conducted an experimental study of the accuracy and precision of the balance used to weigh the analytical

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standard. The balance used to measure the analytical standard was located on a laboratory bench top in a busy location of the analytical lab. The lab was located on an upper floor of the QC laboratory building. Multiple weighings of typical standard weights at the lower calibration limit of the balance were performed according to the approved weighing procedure. All weighings were documented in controlled laboratory notebooks, including witnessing and verification by trained personnel. Mean and standard deviation of weighings were calculated. Results indicated higher than expected variation, confirming the initial reports from QC.

Observation of analysts performing the weighings also suggested that the placement of the standard weight on the balance pan affected the weight data. The weighing procedure did not require that the sample to be weighed be placed in the center of the balance pan.

A CAPA was developed, based on these experimental data and associated observations, as well as the risk analysis indicating the importance of the analytical standard weighing process.

3.4.2 CAPA for the problem

As the ICH has stated, a "pharmaceutical company should have a system for implementing corrective actions and preventive actions resulting from the investigation of [. . .] trends from process performance and product quality monitoring."[18] Such a system came into action as a result of the investigation into the illustrative problem presented in this chapter. Because the variability of data had not yet failed specifications, the CAPA plan highlighted the preventive actions.

The preventive actions focused on upgrading the weighing procedure and facility used for weighing, followed by

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versioning up the relevant SOPs, as well as associated changes in support of the laboratory procedure changes. Table 3.3 outlines the CAPA plan approved by management.

This section discussed the development and implementation of a CAPA plan to respond to the results of the investigation. All the changes to the weighing facility and equipment described in the plan were completed. These included relocation of the weighing of the analytical standard

Table 3.3 **CAPA plan for the illustrative problem**

1.	The first step would include changes to the weighing facility and equipment: ■ The weighing area for the analytical standard would be relocated. The new area would provide virtual isolation from personnel traffic during the weighing process. ■ The balance would be retrofitted with a protective shield to further protect the weighing pan from air drafts during the weighing procedure. ■ The balance would be relocated to a stand-alone vibration-free table.
2.	The calibration procedure for lab balances would be critically reviewed. Changes to the SOP would be proposed as appropriate.
3.	The weighing procedure for samples would be critically reviewed. Changes to that SOP would be proposed as appropriate.
4.	Both procedures would be revised as necessary. In light of the criticality and complexity of the problem, it was decided to use the step-by-step real-world challenge for both SOPs.
5.	Once all recommended changes and revisions were made, an experiment to evaluate changes would be conducted. Test results would be compared to the previous experimental data that characterized current balance performance.
6.	Training on the revised SOPs would be conducted as necessary.
7.	A final report summarizing the above would be appended to change management documentation as necessary.

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to a new area with less personnel traffic, placement of the balance on a stand-alone low vibration table, and installation of a protective enclosure around the balance pan to restrict air drafts. Use of the new protective shield required a revision of the weighing procedure. Training in the use of the weighing procedure was also required.

An important implication of these changes was the necessity of revising SOPs, including the calibration and the weighing procedures. The next session highlights the factors included in the revision of the calibration SOP and the critical review of this revision.

3.4.3 Critical review of the calibration SOP

A manufacturing or lab system in a regulated framework must be demonstrably in control. Any piece of equipment that is part of that system must function according to standards. Because of normal wear and tear, the equipment will tend to deviate from those standards. Equipment calibration and preventive maintenance programs are the method to maintain acceptable equipment performance.

As seen in the CAPA plan, the criticality of the weighing procedure necessitated a review of the balance calibration requirements, standards, and guidance.[19] The requirements included FDA predicate rules for calibration and the documentation of calibration activities, and internationally recognized standards for calibration. The guidance included FDA recommendations for a calibration SOP, and the directions to be gleaned from FDA inspectional observations and warning letters addressing the failure to meet these requirements, standards, and procedures.

Among regulatory documents supporting calibration, FDA requires calibration of equipment and instruments for all

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regulated areas, including good laboratory practice (GLP), GMP, blood processing, medical devices, and tissue processing. The agency also requires written procedures for calibration, and documentation of the calibrations (Table 3.4).

The process of calibrating equipment or instruments involves measurement standards, the calibration process itself, and the device. Measurement standards include the

Table 3.4 FDA predicate rules for calibration

Regulation	Calibration Predicate Rule	SOP Predicate Rule
21CFR58.63	(a) Equipment used for the generation, measurement, or assessment of data shall be adequately tested, calibrated and/or standardized.	(b) written standard operating procedures [. . .] shall set forth in sufficient detail the methods, materials, and schedules to be used.
21CFR211.68	(a) Equipment [. . .] shall be routinely calibrated.	[. . .] according to a written program designed to assure proper performance.
21CFR211.160; § 211.194	(b) Laboratory controls shall include: (4) The calibration of instruments, apparatus, gauges, and recording devices at suitable intervals.	[. . .] in accordance with an established written program.
21CFR606.60; § 606.160.	(a) Equipment used in the collection, processing, compatibility testing, storage, and distribution of blood and blood components shall be [. . .] calibrated on a regularly scheduled basis.	(b) Records shall be maintained that include, but are not limited to, the following when applicable: (5) Quality control records: (i) Calibration and standardization of equipment.

(*Continued*)

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Table 3.4 (Continued)

Regulation	Calibration Predicate Rule	SOP Predicate Rule
21CFR820.72(a)	Each manufacturer shall ensure that all inspection, measuring, and test equipment, including mechanical, automated, or electronic inspection and test equipment, is suitable for its intended purposes and is capable of producing valid results.	Each manufacturer shall establish and maintain procedures to ensure that equipment is routinely calibrated, inspected, checked, and maintained.
21CFR1271.200; § 1271.180	(c) You must routinely calibrate according to established procedures and schedules.	(a) You must establish and maintain procedures.

concepts of reliability, precision, and accuracy. FDA regulations require that equipment be calibrated according to written procedures that include measurement standards for precision and accuracy.[20]

Consider a balance, an instrument used to measure the weight of the product. Several questions arise: Is it a precise instrument? Is it an accurate instrument?

Regarding *precision*, FDA has stated that it "indicates a relative degree of repeatability, i.e., how closely the values within a series of replicate measurements agree with each other."[21] In general, reliability is inversely related to precision.

The National Institute of Standards and Technology has defined *accuracy* and *bias* as follows:

> Accuracy is a qualitative term referring to whether there is agreement between a measurement made on an object and its true (target or reference) value. Bias is a

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quantitative term describing the difference between the average of measurements made on the same object and its true value."[22]

Calibration weights are classified in accordance with the recommendations of the International Organization of Legal Metrology.[23] Classes of weights include E1, E2, F1, F2, M1, M2, and M3, ranging from the highest accuracy weights (E1; maximum error at 1 kg is ±0.5 mg) to the lowest (M3; maximum error at 1 kg is ±500 mg). The higher-class weights are far more expensive than the lower-class weights. Each weight class is "traceable" – tested against a standard of higher accuracy (i.e., the next higher weight class).[24]

Speaking in general of a written procedure for the calibration of equipment, FDA has suggested[25] that the SOP include the sections listed in Table 3.5.

From a compliance standpoint, the eight topics listed in Table 3.5 are important. FDA has made inspectional observations on organizations that have not adequately addressed these topics. As an example of the failure to address the frequency of calibration, and its GXP implications, see the FDA Warning Letter to International Biologicals

Table 3.5 Outline of SOP for the calibration of equipment

1. Purpose and scope
2. Frequency of calibration
3. Equipment and standards required
4. Limits for accuracy and precision
5. Preliminary examinations and operations
6. Calibration process description
7. Remedial action for product
8. Documentation requirements

dated 12 June 1998: "There were no procedures outlining the frequency for calibrating the scales."[26] For an instance of not addressing required standards, see FDA Warning Letter to BTI Filtration dated 7 February 2007: ". . . your firm does not include the specifications for the equipment requiring calibration."[27]

For an example of failing to address limits for accuracy and precision, see FDA Warning Letter to ChemSource, dated 15 November 2002:

> The inspection revealed that your laboratory equipment calibration program is inadequate in the following ways: [. . .] Failure to have written procedures describing specific calibration instructions, and limits. [. . .] Failure to conform to the USP Section <41> for weight and balance determination.[28]

As an example of the failure to incorporate remediation steps in the calibration procedure, see FDA Warning Letter to B. Braun Medical dated 15 March 2006:

> . . . personnel knowingly utilized [. . .] several balances that were [. . .] out of calibration [. . .] In fact, your written procedures do not discuss initiating an investigation to determine whether product may have been impacted, nor discuss corrective actions for equipment that does not meet acceptable tolerance limits.[29]

For an instance of not meeting documentation requirements, see FDA Warning Letter to Dale Dental, dated 14 October 2004, pointing out the "Failure to [ensure] that calibration records are maintained."[30]

The calibration procedure involved in the illustrative study presented in this chapter was found to meet all these

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standards and regulations. However, prior observations that the location of the standard weight on the balance pan affected weight data suggested that the calibration procedure should be more carefully controlled. A target weight location "X" was inscribed in the balance pan to better define the placement of the standard weight for calibration. This change necessitated a revision to the calibration SOP used by calibration technicians.

As the weighing procedure was reviewed, the following revisions were indicated:

- Requirements to use the specified balance in the new weighing facility for weighing of analytical standards;
- New steps for correct operation of the protective shield enclosure around the balance weighing pan;
- Requirement to place sample to be weighed on the target "X" location on the balance pan.

The revised procedures were drafted and critically reviewed by a step-by-step real-world challenge.

This section discussed the review and revision of SOPs as part of the implementation of a more general CAPA project. It focused especially on the revision of the calibration SOP and the critical review that was part of this revision. The next section addresses the testing of the efficacy of the CAPA and the documentation of the results.

3.4.4 Testing and documenting the changes

As Gamal Amer has put it, a successful CAPA must "make necessary changes to reduce risk or eliminate it." Moreover, it is necessary to "track and evaluate the actions taken to ensure that no additional or different risk was introduced."[31] This calls for the testing of the efficacy of the changes made,

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after which the completed project is fully documented, and final approval is sought.

An experimental study was conducted to evaluate the effects of the facility changes, revised calibration procedure, and revised weighing procedure. The same procedure as previously used to evaluate and characterize the balance prior to changes was used. The balance was recalibrated using the new calibration procedure. Multiple weighings of typical standard weights at the lower calibration limit of the balance were performed according to the revised weighing procedure. All weighings were again documented in controlled laboratory notebooks including witnessing and verification by trained laboratory personnel. Mean and standard deviation were calculated. Expectations were that results would be statistically equivalent or improved, relative to pre-change results. Results indicated equivalent accuracy and lower variation as reflected in lower standard deviations.

All the changes were initiated for routine use in support of commercial manufacturing. The responsible project manager developed a document describing all associated changes (Table 3.6).

When the change management document was completed, it was affixed to the procedure change documentation as supporting evidence for the change. Implementation of the change required management approval, SME approval, and supporting experimental data.

3.5 Conclusion

This chapter addressed changes to process as well as the revision of SOPs. In order to ensure that the revision of the SOP adds value, it should be subjected to critical review. A

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Table 3.6 Change management documentation

1. Description of changes	All changes listed above were described. These included the facility changes, equipment changes, calibration procedure change, and weighing procedure change.
2. Reason for change	These changes were due to observations and testing that suggested that product potency seemed to have excessive variation. Evaluation of current facilities and procedures indicated that improvements could be quickly and easily accomplished. The importance of the weighing procedure in determination of potency of commercial product was noted.
3. Risk analysis and evaluation	The formalized risk analysis of the potency determination process – including weighing procedure and associated activities – was documented. The risk analysis document identified specific activities to lessen identified risks.
4. Change management plan	Requirements and considerations to implement the described changes included: ■ **Agreement with standards and internal policies**: These included the review of FDA and internal requirements. ■ **Procedure changes**: Changes to two operational SOPs were identified: 1) Calibration procedure; and 2) Sample weighing procedure. ■ **Regulatory documents affected**: There were no regulatory documents affected by this change. Calibration procedures and weighing procedures are not filed as regulatory documents. ■ **Testing requirements**: The comparative testing and acceptance requirements for testing were specified. The treatment of statistical data was described. ■ **Other requirements**: Training of calibration personnel and laboratory analysts on respective new SOPs was described. In addition, training of laboratory analysts was enhanced to include a skill demonstration assessment (SDA) using the revised procedure described above. ■ **Ongoing monitoring**: Laboratory management would conduct timely ongoing recording of product potency data to continually monitor and confirm the efficacy of the above changes. ■ **Communication to affected areas**: Areas affected by the changes described and associated work were identified. This included responsible CAPA management who initiated the original investigation addressing high potency variation. Laboratory facility engineering drawings were also updated to reflect changes.

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range of approaches to the critical review of procedures, in terms of increasing credibility of the review findings, was presented. Management must select among these approaches, weighing the benefits of increasing credibility against the costs of increasing rigor of the approach appropriate for the level of risk of the procedure.

An illustrative problem involving a laboratory weighing procedure was considered, including physical facilities that might be implicated in the problem. This led to the development and implementation of a CAPA project, including changes to laboratory SOPs. FDA regulations for equipment calibration and the associated SOPs were examined. The internal calibration procedure was evaluated for consistency with FDA requirements and technical quality. It was noted that the laboratory weighing procedure must also be reviewed for technical quality. Based on all of the above, the procedural changes were implemented. Finally, the changes brought about through the CAPA by comparative experimental testing were evaluated, and the results were documented.

Critical review of procedures will prove useful in FDA regulated industry. Whatever the origin of the proposal to revise the procedure – whether it is the regularly scheduled biennial revision of a life-cycle document, or a corrective action in response to an investigation into non-conformance, etc. – revision should add as much value as possible in terms of the relative costs and benefits of the various approaches to critical review. This cost/benefit analysis must be informed by a risk assessment of the change. Adding value to procedures makes business sense. It also makes compliance sense, because it affirms that the document and its associated real-world process are both in control. Employing one of these approaches to the critical review of procedures will surely contribute to process control in the lab or manufacturing environment.

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3.6 Notes

1. According to the FDA, "Standard Operating Procedure (SOP) means a written method of controlling a practice in accordance with predetermined specifications to obtain a desired outcome." See, for instance, FDA (2006).
2. These changes usually do not include the correction of typographical errors, the addition of clarifying statements, the updating of organizational names, etc. to currently implemented procedures. Since an SOP is a life-cycle document, such "cosmetic" changes could well wait until the next regularly scheduled procedure review.
3. See FDA (1987).
4. The ISO standard 9000:2000 defines "validation" as "confirmation through the provision of objective evidence that the requirements for a specific intended use or application have been fulfilled . . ." See ISO 9000 (2000).
5. See William R. Shadish, Thomas Cook, and Donald Campbell (2002); see also James H. McMillan (2007).
6. On the Rosenthal effect, see Robert Rosenthal (1966); also see Rosenthal (1998).
7. See William R. Shadish, Thomas Cook, and Donald Campbell (2002).
8. See, for instance, N.N. Radaev (2004).
9. As H. Gregg Claycamp (2006) has put it in his presentation to the CDER Advisory Committee for Pharmaceutical Science (ACPS), there are a number of kinds of risk for a company – strategic risks, operational risks, financial risks, compliance risks, competitor advantage, company viability, shareholder harm, patient harm, etc. This chapter focuses on quality risks.

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10. See International Conference on Harmonisation (ICH) (2005).
11. See G.R. Kermode and S. Sivaloganathan (2000).
12. See 42 CFR 493.17. For an overview of CLIA, see Patrick Rivers *et al.* (2005).
13. See ICH (2005) op cit.
14. See Roger Nosal and Tom Schultz (2008), writing on behalf of the Product Quality Life-cycle Implementation (PQLI) initiative of the International Society for Pharmaceutical Engineering (ISPE); also Thomas Garcia *et al.* (2008). As Matthew Ferrier (2006) has defined it, a critical component of a process is "a component within a system where the operation, contact, data, control, alarm, or failure will have a direct impact on the quality of the product," while a non-critical component is "a component within a system where the operation, contact, data, control, alarm, or failure will have an indirect impact, or no impact on the quality of the product." We can interpret "quality" in this context to mean the SISPQ of the product.
15. See also Roger Nosal and Tom Schultz (2008), op. cit. David Fetterolf (2007) has provided an illustration of the measurement of criticality, where each parameter of a system is assessed for its potential to affect the applicable process controls or quality attributes. Each parameter is given a numerical rating based on the likelihood and potential magnitude of impact. The parameters that have the highest likelihood and potential to affect the process are entered into range-finding studies and the outcome of the studies is the relationship between the parameter's normal *operating range* (r_o, control space) and its proven *acceptable range* (r_a, design space). The normal operating range is the range at which the parameter is typically controlled

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during routine operations, usually the range found in manufacturing instructions. It takes into account minimum and maximum values tested during initial development and a review of process history, which shows the capability of operators, facility, equipment, and utilities. The proven acceptable range is defined by minimum and maximum values for each parameter found during the range-finding studies. Range-finding studies are often designed such that the ranges studied are two or three times the normal operating range. If a parameter's operating range is less than two times its acceptable range, i.e. $r_o < 2 \times r_a$, this indicates that a deviation to the normal operating range would likely result in a failure to meet an in-process control, in-process specification, or failure of the batch.

16. ICH (2005) op. cit. As Kevin O'Donnell and Anne Greene (2006) have expressed it:

> risk events can have multiple causes, with multiple associated risks, some less important that [*sic*] others. This can result in formal risk management activities becoming costly and quite labor-intensive exercises, and should, therefore, be targeted at the most *complex* or *critical* issues" (italics added).

17. 21 CFR 211.192, "Production Record Review." See also Gamal Amer (2008) on the "two types of quality events associated with risk."
18. See ICH (2008).
19. A similar critical review of the weighing SOP itself was required, but not included here. In addition, that review took into account the guidance provided by *US Pharmacopeia* <1251>.

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20. For instance, 21 CFR 820.72(b). See Andrew Lowery *et al.* (1996). According to National Institute of Standards and Technology (NIST) (2003):

> Calibration is a measurement process that assigns values to the property of an artifact or to the response of an instrument relative to reference standards or to a designated measurement process. The purpose of calibration is to eliminate or reduce bias in the user's measurement system relative to the reference base.

Available from: *http://www.itl.nist.gov/div898/handbook*

21. Lowery et al. (1996) ibid.
22. See NIST (2003) op. cit. The FDA has defined accuracy as "the measure of an instrument's capability to approach a true or absolute value. Accuracy is a function of precision and bias." Bias, in turn, is defined as "a measure of how closely the mean value in a series of replicate measurements approaches the true value;" see Lowery et al. (1996) op cit.
23. See International Organization of Legal Metrology (2004).
24. As FDA has stated, "Calibration standards used for inspection, measuring, and test equipment shall be traceable to national or international standards;" see 21 CFR 820.72, "Inspection, measuring, and test equipment."
25. Lowery et al. (1996), op cit.
26. Available from: *www.fda.gov/foi/warning_letters/archive/1857b.pdf* See also FDA Warning Letter to American Blending and Filling dated 27 September 2001, pointing out the "Failure to establish written procedures for the calibration of compounding and laboratory equipment. Instruments utilized in the

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29. Available from: *www.fda.gov/foi/warning_letters/archive/*g*5817d.pdf*
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31. See Gamal Amer (2008).

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4

Working with standard operating procedures (SOPs)

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Abstract: The preceding chapter established the central role of a standard operating procedure in the regulated process. The first part of this chapter presents a template for the development of a SOP, including the relation of a process map (flowchart) to the SOP. The second part illustrates the completion of that template with a cleaning and sanitizing procedure. This will also involve a review of the process of cleaning and sanitizing of facilities for GMP compliance.

Key words: allowable levels, bioburden, cleaning, GMP zones, good documentation practices, procedure (SOP), responsible (party), safety precautions, sanitization.

4.1 Introduction

Let us briefly review the critical role that standard operating procedures (SOPs) play in regulated industry:

(a) SOPs are "process controls;" they control the execution of processes;

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(b) SOPs can control several kinds of process – a person-to-machine process, a person-to-paper process, a person-to-person process, or some combination of these;

(c) SOPs promote clarity about what the task is, as well as the organizational and environmental settings for task performance;

(d) SOPs define the resources that are necessary for each task, and the personnel responsible for completing the tasks;

(e) SOPs identify the sequencing of the tasks within a given process, and the standards that define the satisfactory completion of the tasks; and

(f) SOPs are a regulatory requirement in manufacturing in the life sciences industry.[1]

In fulfilling these roles, SOPs have a typical form that can be displayed in a template.

4.1.1 Template for an SOP

An SOP has four major sections:

1. Introductory material;
2. Actions (tasks) and responsibilities;
3. Approvals;
4. Version history.

The *introductory material* includes the SOP's purpose, the scope of its application, any acronyms and definitions that will clarify its content, any references to other procedures or controlled documents that are relevant to the content, any materials that are involved in the process, safety precautions that must be observed in executing the procedure, and any policy issues. This is schematized in Figure 4.1. If this SOP

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Good manufacturing practices procedure			
Subject		**SOP#**	**Version**
xxx		**xxx.xxx**	**x.0**
Purpose:	This procedure provides detailed instructions for...		
Scope:	This procedure applies to...		
Acronyms:			
Definitions:			
References:			
Materials:			
Safety precautions:			
Policy:			

Figure 4.1 Introductory material of an SOP

includes references to other SOPs, this can raise problems of updating. The question is how to ensure that the updating of this SOP is reflected in the updating of the references in other SOPs.[2]

The second section, *actions and responsibilities*, contains the listing of the procedure's actions (tasks) and the personnel responsible for executing each of these tasks. Each of these tasks is necessary for the completion of the process. The tasks are listed in a sequential order; each task is necessary for the following task. All these tasks, taken together and correctly executed, are sufficient for the successful completion of the process. A parallel column indicates the personnel (job title) who are responsible for the execution of each task. There must be one and only one job title listed for each task (Figure 4.2).

John Avellanet has nicely summarized the process of developing the tasks and responsibilities section of a SOP:

> . . . before writing a standard operating procedure or policy, draft a flowchart that highlights critical

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Good manufacturing practices procedure			
Subject		SOP#	Version
xxx		xxx.xxx	x.0
		Procedure	
Responsibility		Action	

Figure 4.2 Actions and responsibilities

> decision points and potential controls. Implement this flowchart. Then use mock audits or test runs to assess the controls and the business flow. Refine and test again . . . Finally, write and wordsmith the detail behind the flowchart.[3]

How will the content of the flowchart be assembled? There are several options – employee behavior can be directly observed, critical incidents can be reviewed (a case-study approach), questionnaires can be developed (and, if so, can be distributed to various employees), subject matter experts (SMEs) can be interviewed, etc. An illustrative flowchart for a Notice of Event (NoE) is shown in Figure 4.3a and deviation investigation process is shown in Figure 4.3b. The risk levels for the illustrative event range from 1 = highest to 3 = lowest.

Once the flowchart has been finalized, and approved by management, it can be translated into the documentary form of the SOP. Many times, this translation will amount to the discursive writing out of the process map captured in Visio. Any time the documentary form deviates from the process map, the latter will prevail.

Approvals is the third section of the procedure, allowing each employee who must approve the procedure to do so (Figure 4.4).

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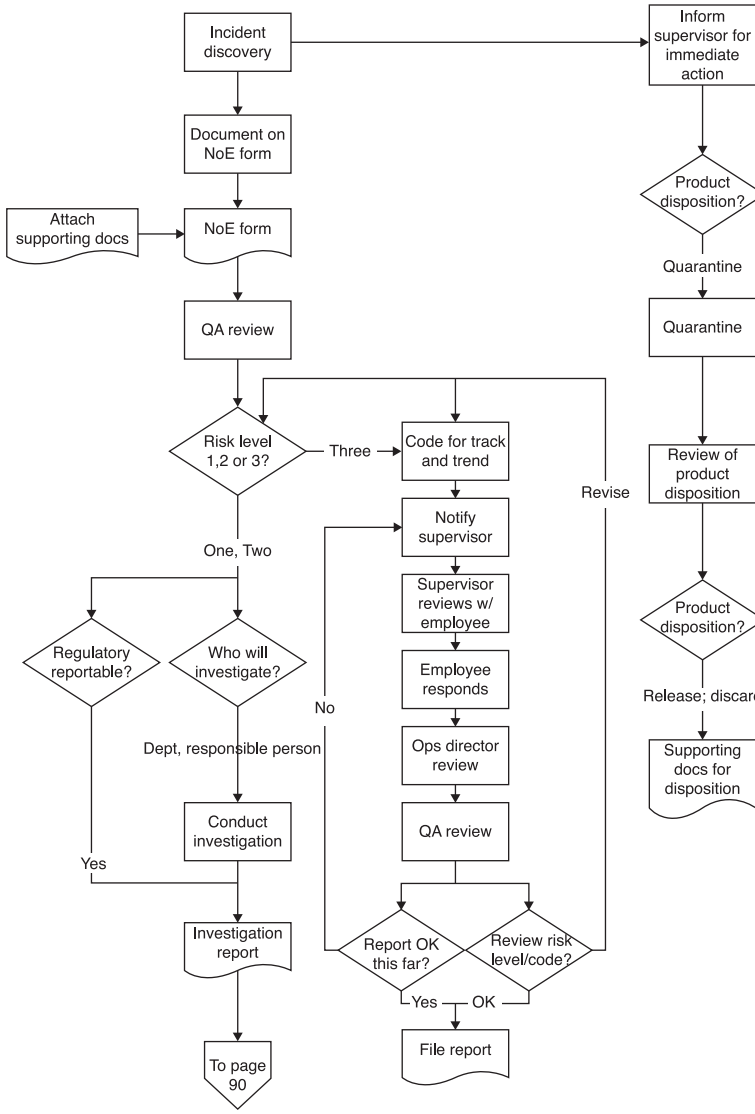

Figure 4.3 Notice of event (NoE) and deviation investigation (*Continued*)

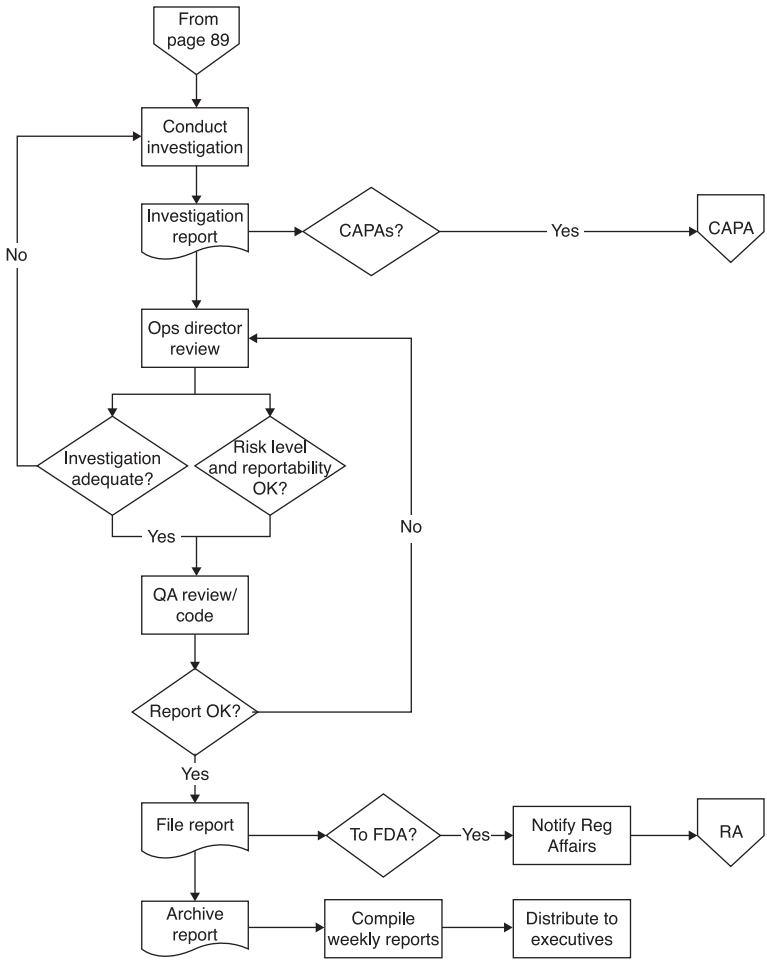

Figure 4.3 ***Continued***

The fourth section includes the *version history* of the procedure, which facilitates the reconstruction of that history when needed.

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Good manufacturing practices procedure		
Subject	**SOP#**	**Version**
xxx	**xxx.xxx**	**x.0**

Approvals	
Title	Signature

Version history				
Version	x.0	Supersedes version		Date:
Work request #		CA #		
Reason for change:				

Figure 4.4 Approvals and version history of an SOP

4.2 The process of cleaning and sanitizing of facilities

Cleaning and sanitizing involves both issues of operational efficiency – the avoidance of unnecessary rework – and issues of regulatory compliance. Facility cleaning is the process of removing soils and other impurities from a surface, for instance a wall, ceiling, or floor. Facility cleaning also includes furnishings in a room such as benches, tables, cabinets, etc. Cleaning activities are followed by sanitizing activities. Sanitizing activities are the process of reducing the bioburden, the number of microorganisms on a cleaned surface, to a specified level.

Cleaning activities and sanitizing activities prevent product contamination, as well as to ensure regulatory compliance. As the *Code of Federal Regulations* (CFR) stipulates, facilities used in the manufacture, processing, packing, or holding of a drug product must be maintained in a clean and sanitary condition, so as to prevent the contamination of equipment,

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components, drug product containers, closures, packaging, labeling materials, or regulated products.[4] Consider another regulated area. Regarding the manufacture of human tissue products, the CFR states that any facility used in the manufacture of human cells, tissues, and cellular and tissue-based products (HCT/Ps) must be maintained in a clean, sanitary, and orderly manner, to prevent the introduction, transmission, or spread of communicable disease.[5]

The FDA has requirements for cleaning and sanitizing for a number of regulated processes that are listed in Table 4.1.[6]

Any surface or area that might adversely impact the safety, identity, strength, purity, and quality (SISPQ) of the regulated product must be cleaned and sanitized. This includes the various surfaces of buildings and facilities, equipment and utensils, and containers and closures. With respect to facilities, rooms and zones of buildings are typically classified in terms of levels of particulate matter allowable in the air or on surfaces.

Moreover, there are three major categories of soils and other impurities that must be removed from a surface. These are:

1. product from a previous manufacturing run;
2. bioburden, such as various microorganisms; and
3. the cleaning and sanitizing agents from previous cleaning activities.

Table 4.1 FDA requirements for cleaning and sanitizing

Regulated process	21 CFR Section	CFR Heading
Food	§ 110.20	Plant and grounds
Food	§ 111.15	Sanitation requirements
Drugs	§ 211.56	Sanitation
Biologicals	§ 600.11	Physical establishment
Blood	§ 606.40	Facilities
Human Tissues	§ 1271.190	Facilities

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Any of these soils can contaminate the regulated product and must be reduced to an acceptable level.

4.2.1 Cleaning and sanitizing activities are controlled by SOPs

Facilities are to be cleaned and sanitized according to cleaning and sanitizing SOPs. The CFR stipulates that there must be written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used in cleaning the buildings and facilities. The CFR continues "such written procedures shall be followed."[7] An illustrative example of such a cleaning and sanitizing procedure is included in the next part of this chapter.

Cleaning and sanitizing of facilities occur according to specific schedules that are typically appended to the cleaning and sanitizing SOP. These schedules allow the rooms to be used for production purposes, while still permitting the rooms to be cleaned and sanitized. Not only are the rooms scheduled for cleaning and sanitizing, but the specific surfaces within each room are also scheduled. For example, cleaning schedules for ceilings are different from cleaning schedules for floors. Ceilings tend to bear less soil than do floors, and are in less close proximity to the product. Thus floors will be the focus of more intensive and frequent cleaning and sanitizing efforts than will ceilings. This differential level of effort will be reflected in the cleaning and sanitizing schedules for each room. Illustrative examples of a cleaning schedule and a sanitizing schedule follow as Figures 4.5(a) and 4.5(b).

All cleaning and sanitization activities must be documented as soon as completed, in the appropriate cleaning log and

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Cleaning schedule, Room XXX		
Interval	**Surface**	**Cleaning activity**
Daily	Ceiling	
	Walls	
	Furnishings	
	Floors	
Weekly	Ceiling	
	Walls	
	Furnishings	
	Floors	
Monthly	Ceiling	
	Walls	
	Furnishings	
	Floors	

Sanitizing schedule, Room XXX		
Interval	**Surface**	**Sanitizing activity**
Daily	Ceiling	
	Walls	
	Furnishings	
	Floors	
Weekly	Ceiling	
	Walls	
	Furnishings	
	Floors	
Monthly	Ceiling	
	Walls	
	Furnishings	
	Floors	

Figure 4.5 Room XXX: cleaning and sanitizing schedules

sanitizing log for that room (Figures 4.6(a) and 4.6(b)). All log entries will comply with good documentation practices. For any day of the month when cleaning and/or sanitizing activities occur, the employee who has completed that activity will print his/her name in the log

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Cleaning log, Room XXX

Month_____ Year_____

Completed by:	Initial	Date	Shift	Freq	Agent	Lot	Expir.

Supervisor review by:_____ Date:_____
QC review by:_____ Date:_____

Sanitizing log, Room XXX

Month_____ Year_____

Completed by:	Initial	Date	Shift	Freq	Agent	Lot	Expir.

Supervisor review by:_____ Date:_____
QC review by:_____ Date:_____

Figure 4.6 Room XXX: cleaning and sanitizing logs

using a black (or blue) ink pen. Next, the employee will initial and date the entry next to his/her name. Then the employee will indicate the shift during which the activity occurred, and the scheduled frequency – either D = Daily, M = Monthly, or S = Special. Finally, the employee will indicate the cleaning or sanitizing agent used, its lot number, and its expiration date.

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If there is a correction to a log entry, the erroneous entry will be struck out with a single line using a black (or blue) ink pen, the correction will be entered, and initialed and dated. The cleaning and sanitizing logs for each room will be reviewed by the supervisor of the cleaning and sanitizing staff according to the review schedule. After determining that the logs are complete and correct, the supervisor will countersign and date. The logs countersigned by supervision will be reviewed by quality control (QC) staff. After determining that the logs are complete and correct, the QC staff member will countersign and date. The completed, countersigned and dated logs will be retained by the maintenance department.

According to FDA regulations, it is the supervisors who must perform assigned functions in such a manner as to provide assurance that the regulated product has the SISPQ that it purports or is represented to possess. The CFR indicates that non-supervisory personnel, by contrast, must simply perform assigned functions. Thus the personnel responsible for the efficacy of the cleaning and sanitizing activities are supervisors, not operators.[8]

Cleanliness of facilities and equipment is typically determined by visual inspection.[9] Visual cleanliness is defined as the absence of visible residue. Factors that can impact the perception of visual cleanliness include the observer's distance from the surface, the viewing angle, light intensity, the color of the residue and the surface color, human differences in eyesight, etc.[10] The adequacy of the cleaning program should be investigated, should visual inspection indicate residue remaining after cleaning.

Environmental monitoring (EM) data indicate the quality of the sanitizing activities. Each air and surface sample must be evaluated by comparison to the established alert or action levels. This comparison as well as monitoring schedules,

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sampling frames, etc. will be specified in the relevant EM procedure. If the alert level is exceeded for a given sample, this suggests that the specific environment is approaching an action level. Should the action level be exceeded, this calls for a comprehensive investigation. The adequacy of the cleaning and sanitizing program should be one of the factors investigated as potentially contributing to the excursion.

4.3 An illustrative example of a cleaning and sanitizing SOP

An illustrative example of an SOP for a cleaning and sanitizing program is included in this part of the chapter (Figures 4.7). Since its purpose is to illustrate what a procedure looks like as the SOP template is filled out, it is intentionally schematic.

Good manufacturing practices procedure

Subject	SOP#	Version	
Cleaning and sanitizing GMP areas	xxx.xxx	1.0	

Purpose:	This procedure provides detailed instructions for the cleaning and sanitizing of GMP areas within the X facility.	
Application:	This procedure applies to all cleaning and sanitizing activites within the GMP areas of the X facility.	
Acronyms:	**CFU/m^3**	Colony forming units per volume
	CFU/m^2	Colony forming units per surface area
	GMP	Good manufacturing practices
	MSDS	Material safety data sheet
	SISPQ	Safety, identity, strength, purity, and quality of a drug product
	PPE	Personal protective equipment

Figure 4.7 Cleaning and sanitizing SOP

(*Continued*)

Good manufacturing practices procedure

Subject	SOP#	Version
Cleaning and sanitizing GMP areas	xxx.xxx	1.0

Definitions:	**Allowable level of airborne microorganism** is the CFU/m^3 permitted for that GMP zone. **Allowable level of surface microorganism** is the CFU/m^2 permitted for that GMP zone. **Facility cleaning** is the process of removing soil and other impurities from a surface, for instance a wall, ceiling, or floor. **Facility sanitizing** is the process of reducing the bioburden, the number of microorganisms on a cleaned surface, to a specified level. **GMP zones** are classified in terms of levels of particulate matter allowable in the air and/or on surfaces, ranging from zone A, least particulate matter allowable, to zone C.
References:	• SOP on cleaning overview. • SOP on sanitization overview. • SOP on approved cleaning agents. • SOP on approved sanitizing and sporicidal agents. • MSDS for each cleaning and sanitization agent. • SOP on cleaning and sanitization logs. • SOP on respirator protection, etc.
Materials:	• Approved cleaning agents: X, Y, Z. • Approved sanitizing agents: A, B, C. • 70% isopropyl alcohol. • Approved mops and covers. • Approved mop buckets. • Approved cleaning and sanitizing carts. • Lint-free wipes.
Safety precautions:	• Wear PPE approved gloves and safety glasses. • Avoid eye contact, skin contact, and inhalation of mist. • Use a Racal breathing hood when required. • Liquid splashing on floors may result in trips, slips, and falls. • Use "Wet Floor" signs when necessary. • Do not overfill mop buckets. • Dispose of glass in the broken glass bin only. • Use only a locking ladder when cleaning/sanitizing. • Make sure to keep both feet squarely on ladder. • If ladder is wet, dry with towel. • Use proper lifting technique (legs, not arms or back) when emptying trash or moving heavy containers.
Policy:	• Facility cleaning must remove any soil or other impurities that might impact the SISPQ of the product, from the various surfaces of buildings and facilities. • Facilities sanitizing must reduce the bioburden on the various surfaces of buildings and facilities to an acceptable level so as to prevent any impact on the SISPQ of the regulated product.

Figure 4.7 *Continued*

Good manufacturing practices procedure

Subject	SOP#	Version
Cleaning and sanitizing GMP areas	xxx.xxx	1.0

		Procedure
Responsibility		Action
	A.	Preparation of cleaning and sanitizing solutions
Cleaning staff	1)	Prepare cleaning solution according to specification.
Cleaning staff	2)	Prepare sanitizing solution according to specification
	B.	Daily cleaning activities
Cleaning staff	1)	Clean the areas according to schedule.
Cleaning staff	2)	Clean with overlapping strokes. Use double pail method. Maintain contact time for solution. Clean from top to bottom: • Ceiling • Walls • Work benches, cabinets and equipment • Floors Clean toward the exit of each room.
	C.	Daily wiping activities
Cleaning staff	1)	Wipe surfaces according to schedule.
Cleaning staff	2)	Spray sanitizing solution onto surface. Use dry wipe on small areas at a time. Fold wipe after each stroke to expose clean fabric. Discard the used wipe.
Responsibility		Action
	F.	Monthly cleaning activities
Cleaning staff	1)	In addition to the activites listed under A, B, C above:
Cleaning staff	2)	Clean the floor with detergent to remove any residue, before cleaning with approved cleaning solution.
Contractor staff	3)	Sterilize the room with vaporized hydrogen peroxide (HPV) as needed.

Figure 4.7 *Continued*

Good manufacturing practices procedure

Subject	SOP#	Version
Cleaning and sanitizing GMP areas	xxx.xxx	1.0

	G.	Sanitizing drains
Cleaning staff	1)	All floor drains and sink drains will be sanitized according to schedule.
Cleaning staff	2)	Pour one gallon of sanitizing solution into each drain.
	H.	Cleaning and sanitizing documentation
Cleaning staff	1)	At the completion of cleaning and sanitizing activites for each room, sign and date the appropriate cleaning log.
Cleaning staff	2)	At the completion of sanitizing drains for each room, sign and date the appropriate cleaning log.
Cleaning supervisor	3)	Review the logs for each room according to schedule, and countersign and date.
QC staff	4)	Review the logs for each room according to schedule, and countersign and date.
	I.	Monitoring efficacy of cleaning and sanitizing
QC staff	1)	Monitoring the efficacy of cleaning and sanitizing according to schedule.
QC staff	2)	Conduct air sampling in each room.
QC staff	3)	Use RODAC contact plates to sample surfaces in each room.

Approvals

Title	Signature	Date

Figure 4.7 *Continued*

Good manufacturing practices procedure					
Subject		**SOP#**		**Version**	
Cleaning and sanitizing GMP areas		**xxx.xxx**		**1.0**	
Version summary					
Version	1.0	Supersedes version	None	Date	None
Work request #			CA #	N/A	
Reason for change:		New procedure			

Figure 4.7 *Continued*

4.4 Conclusion

This chapter presented a template for the development of SOPs, including the relation of a process map (flowchart) to an SOP. It then illustrated the completion of that template with a cleaning and sanitizing procedure. This also involved a review of the process of cleaning and sanitizing of facilities for GMP compliance.

4.5 Notes

1. See John DiLollo (2000); also Michelle Rosa (2006); and Irina Colligon and Michelle Rosa (2007).
2. See the discussion in David Porter (2010).
3. See John Avellanet (2008).
4. See 21 CFR 211.56, Sanitation.
5. See 21 CFR 1271.190, Facility cleaning and sanitation.
6. For similar EU and ICH statements, see Jeanne Moldenhauer (2009).

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7. 21 CFR 211.56, Sanitation.
8. 21 CFR 211.25, Personnel qualifications.
9. See Paul Pluta (2009).
10. See Richard Forsyth (2009).

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5

The design phase of the program improvement model

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Abstract: This chapter will begin the discussion of the role of training in ensuring compliance with current manufacturing practices, and in particular, current good manufacturing practices (cGMPs). It is convenient to present the role of training in terms of the program improvement model. This model provides guidance at a fairly high level for program developers, instructional designers, software engineers, etc. as they author and revise their products. There are several application values of the program improvement model. First, the model clarifies and standardizes the process of addressing performance gaps in an organization, allowing best practices to be identified and implemented. Second, this model is widely utilized in various forms in the pharmaceutical industry, which facilitates benchmarking of program development initiatives between organizations.

Key words: ADDIE model, feedback loop, formative evaluation, overview training, performance gap, pilot implementation, program improvement model, scalable, skills training, summative evaluation, training curriculum, training outline.

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5.1 The ADDIE model and the program improvement model

The program improvement model is ultimately derived from the familiar ADDIE model. The phases of the ADDIE model are **A**nalyze, **D**esign, **D**evelop, **I**mplement, and **E**valuate. These phases are sequential – each depends upon the successful completion of the preceding phase. Moreover, the ADDIE model is an iterative feedback model, which means that the results of the Evaluation phase are fed back, closing the loop, facilitating further refinement of the program. If the evaluation shows that a training module has shortcomings – for example, that the objectives of the program do not align with organizational objectives – those shortcomings are fed back to be analyzed again. Further design and development efforts follow, until the program meets organizational needs (Figure 5.1).

The ADDIE model is scalable to all size pharmaceutical, biopharm, and medical device companies. The model can be scaled to various size organizations, and can be fitted to the particular needs of a specific department within the organization on a case-by-case basis, or by an overall decision. As an example of a particular case, once a problem has been identified, investigated, and subjected to a CAPA plan, the decision may be made in the Analysis phase of the ADDIE model to forego the needs analysis of employees' skills and dispositions – these attributes may be well-known and documented, requiring no further analysis. Thus management makes the decision to limit the Analysis phase to a task analysis, that is, to the tasks that have been revised and must be integrated into the learning plans of the affected personnel.

As another example, management may make the overall decision to forego Pilot Implementation – and the associated Formative Evaluation – and roll out the program directly. In

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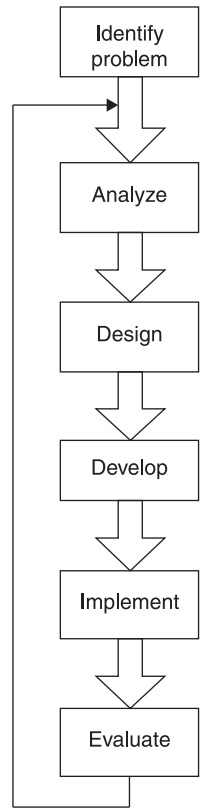

Figure 5.1 The ADDIE model

this instance, the Implementation phase is followed by Summative Evaluation. In both examples, it is a management decision to save costs by limiting the ADDIE model.[1]

The Analysis phase of the ADDIE model identifies a training issue such as a performance gap, a discrepancy between a standard stipulated in a standard operating procedure (SOP) and some employee performance. The performance gap can be addressed by a training program (i.e., a set of training and assessment materials, a qualified trainer, and a training audience).

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This is followed by the Design phase of the ADDIE model, where a carefully planned approach to addressing the performance gap is outlined and approved. This planned approach has three components:

1. fitting the proposed training program (or module) into the larger training curriculum;
2. outlining the proposed training module; and
3. securing management approval of the outlined training program.

If management approves the proposed design, the Development phase of the ADDIE model comes next, where the training program – the training materials and the assessment materials – is developed to address the performance gap.

To anticipate, this is the point where the program improvement model and the ADDIE model diverge from one another. While the Development phase is followed by the Implementation phase in the ADDIE model, there are two paths out of the Development phase in the program improvement model. One leads to Pilot Implementation; the other leads to Final Implementation. In turn, Pilot Implementation leads to Formative Evaluation, while Final Implementation leads to Summative Evaluation (Figure 5.2).

This chapter will examine the three components of the Design phase in turn, focusing attention on an illustrative example of a training module.

5.2 The training module in the larger curriculum

Fitting the proposed training module into the larger curriculum ensures the articulation of this module with all

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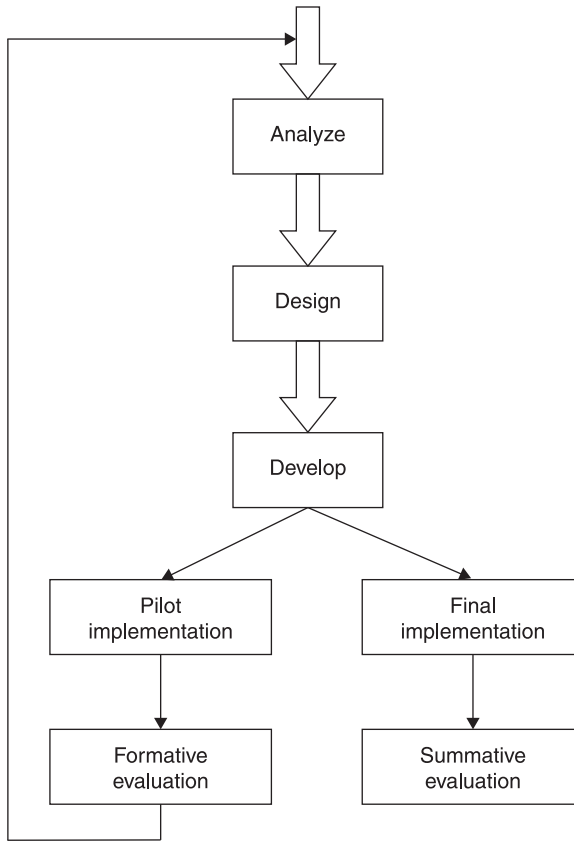

Figure 5.2 **The two paths from the development phase**

other training modules, and the alignment of this module with organizational goals. There are four aspects to this "fit:" the structure of modules; the relationship between the training module and the associated SOP; reducing training modules by consolidation of SOPs; and the relationship between training modules and various regulatory requirements (e.g., FDA, OSHA, EPA, DEA, etc).

The structure of modules: The larger curriculum is comprised of a set of modules that focus the training effort

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on accomplishing organizational goals. The Design phase is where the fit between the proposed training module and the larger curriculum is delineated. This means outlining the structure wherein the training module will fit. Each module includes two training elements, an *Overview Training* element and one or more associated *Skills Training* elements.[2] A module is displayed in Figure 5.3.

In the Design phase, the precise location of the training element – as an Overview Training element or a Skills Training element – is determined. We will briefly review the difference between these two types of elements. Overview Training will be more conceptually focused, while Skills Training will be more task or performance oriented. Concepts tell what a thing is, why it is important; tasks describe how to do something. Concepts provide the "science" for task performance. For example, the tasks involved in sanitizing equipment might be conceptualized as "Reducing the levels of microorganisms and particulates to acceptable limits," thereby minimizing the risk of product contamination from the equipment.

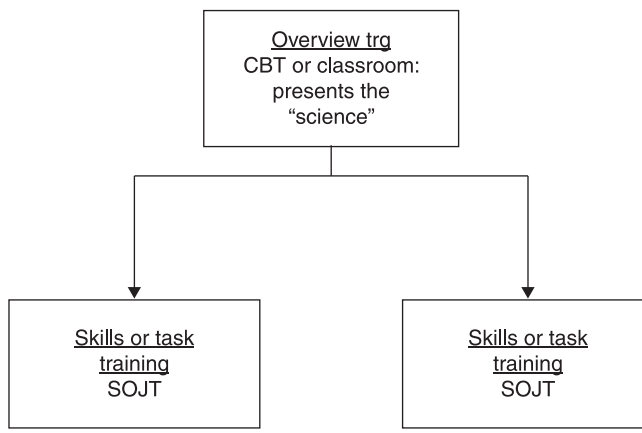

Figure 5.3 Illustrative training module

The Overview Training element will typically be delivered by an instructor in a classroom; if a full-featured Learning Management System (LMS) is available, it may be delivered electronically. There will be an SOP for this Overview Training event. The Skills Training elements will usually be delivered one-on-one by a subject matter expert (SME) who is also a trainer, on the shop floor as a structured on-the-job training (SOJT) event [3]; there will be an SOP for each of the SOJTs in the module.

The Overview Training element includes an assessment of training effectiveness – a Knowledge Transfer Assessment (KTA), for example. The training event is documented in a Training Record where the trainer and trainee concur that the trainee has, or has not, successfully concluded the event. In the case of classroom instruction, this training record is entered into the training tracking system and the entry is verified. In the case of a validated LMS, the training record will be an integral part of the training module and will be electronically entered into the trainee's training history.

Once the Overview Training event is successfully concluded, the trainee goes on to the SOJT events. The several SOJTs are documented in Skill Demonstration Assessments (SDAs), where the trainee's ability independently to perform the task is documented. The SDA is then entered into the training tracking system, and the entry is verified. After all the relevant SDAs are successfully completed, the trainee is qualified, meaning the trainee is ready to perform that module's tasks independently.

Let us consider several examples, displayed in Table 5.1.

The precise fit of each of these modules into the larger curriculum is determined in the Design phase.

A second aspect of the fit between training modules and the larger training curriculum is the relationship between the

Table 5.1 Illustrative training modules

Module	Overview element	SOJT element
Central Weigh Module	Material Management	■ Storage of Raw Materials ■ Dispensing Raw Materials
1st Cleaning Module	Cleaning and Sanitizing I	■ Facility Cleaning
Preparation of Solutions and Buffers	Media and Buffer Preparation	■ pH Measurement ■ Preparing Media ■ Preparing Buffers
2nd Cleaning Module	Cleaning and Sanitizing II	■ CIP (Clean-in-Place) ■ SIP (Sterilize-in-Place)

training module and the associated procedure. That too will be delineated in the Design phase.

5.2.1 How training modules relate to SOPs

There are two ways that a training module can be related to a procedure. The first is directly, where the module trains to the procedure; this is sometimes called "document based training." The second is indirectly, where the training module is mandated in the SOP, but the module does not train to the procedure; this is called "non-document based training." An example of the latter is training in current GMPs, an FDA requirement. The FDA requires that this training be both "current" and "conducted on a continuing basis."[4] These requirements are typically met by training on courseware that is repeatedly offered, say on a quarterly basis, and is also frequently revised to ensure currency. The SOP that

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provides guidance to the GMP regulatory training is, by contrast, relatively fixed.

In Figure 5.4 the procedure is on the left and the training module is on the right. In the case of a procedure like Management Notification, which identifies the routine as well as exceptional situations where employees must notify their management, the module trains directly to the procedure.

In the case of a procedure like Train-the-Trainer (TTT), by contrast, there are several training modules: one trains to the management of the TTT program; another is the courseware for the TTT classroom sessions; and a third is the courseware for the subsequent TTT qualification session. These training modules have different training audiences: the first module – the program management module – has the organization's

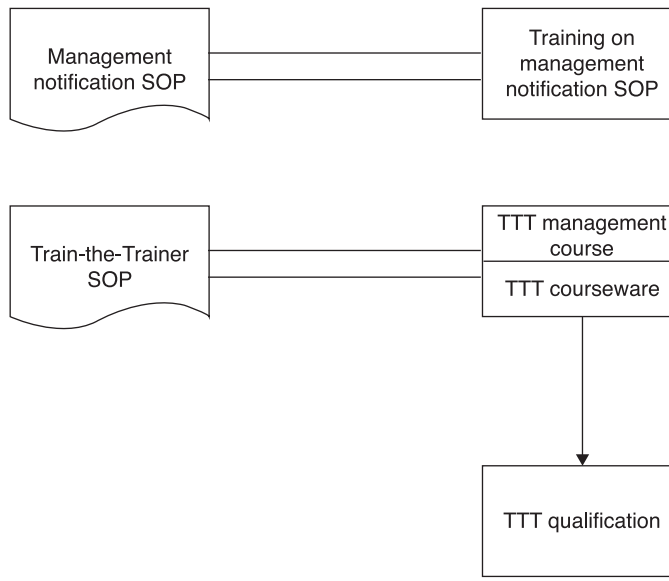

Figure 5.4 Relation of SOP to training model

training unit as its audience; the second and third modules have the prospective qualified trainers as their audience.

Document-based training and non-document-based training must carefully be distinguished in the Design phase; if not, there is the possibility that all the training modules in non-document-based training will be named after the same procedure. We have seen instances where a several-hour classroom session of mandated training had the same name and course number as a one-hour program management course, causing confusion in the training tracking system and among the several training audiences.

It is better to delineate clearly the more complex relationship between training modules and the associated procedure. Figure 5.5 more clearly displays the non-document-based training structure; it is now viewed as similar to a GMP regulatory procedure, where there is training to the procedure and also (a different thing) training on courseware that is mandated by the procedure.

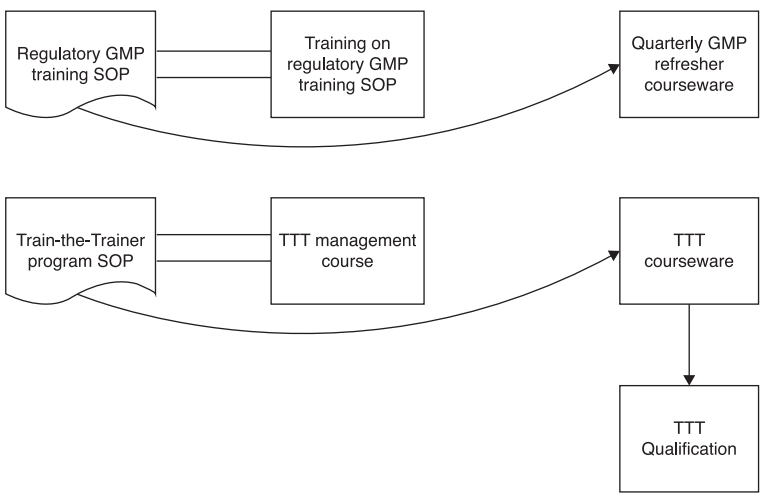

Figure 5.5 Non-document-based training modules

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Now the one-hour training on the management of the TTT program will have its own name in the training tracking system, and the several-hour-long TTT classroom course will have a different name, as will the subsequent TTT qualification session. The two different training audiences can clearly recognize the relevant training modules.

The clear statement of the relation between the training module(s) and the associated procedure should take place during the Design phase of the program improvement model, and will be an important contribution to the ultimate success of the training module.

5.2.2 Consolidate SOPs, reduce the number of training modules

Several training modules can be associated, directly or indirectly, with a single procedure. This suggests that a straightforward means of reducing training time within a training system might be to consolidate SOPs, thereby reducing the number of training modules. However, consolidation (or "streamlining") of SOPs needs to be logical and to eliminate redundancies, not simply reduce the number of SOPs. We will clarify this point.

Consider four examples that illustrate the issue:

1. The FDA requires gowning procedures.[5] Department A has a gowning procedure. Department B has a different gowning procedure. Consolidation of SOPs would remove the redundancies here; Departments A and B would work together toward a single gowning procedure.
2. Department C has a protocol on the use of Equipment-Specific Instructions (ESIs), say involving equipment maintenance manuals. Department D has a different protocol on the same kind of ESIs. Again, streamlining

procedures would remove the redundancies; Departments C and D would work together toward a single protocol on the use of ESIs.

3. Department E has an SOP for operating an autoclave, and another SOP for operating a capping machine. There is no redundancy here; it would be counterproductive to consolidate the two procedures, since they deal with "apples and oranges".
4. Department F has three SOPs and three packaging lines, one procedure for the operation of each line; each includes a brief section on equipment maintenance. There is redundancy here, but not like that in Examples 1 and 2. The redundancy here is in the sections on maintenance. Consolidation of the procedures would remove the sections on maintenance and put them in a maintenance procedure of its own. We will return to this issue in the next section.

Consolidation of SOPs is essentially an issue of correctly writing procedures. Very briefly, procedure writing has six steps, all but the last involving the collaboration of a procedure author (usually a technical writer) and one or more SMEs. First, the SME(s) and the author identify the process to be captured in this SOP. Second, they identify the audience for this SOP. Third, they develop the process map for this process. The process map breaks down the process into its elements, and displays the logical interconnections between the elements. Fourth, the SME(s) and the author "chunk" the process. The chunks are developed from the process map, putting like elements together, and putting unlike elements apart. Fifth, the text of the SOP will be written from the chunks. The author writes this up and the SME(s) reviews the text in light of the intended audience. Finally, the text will be revised by the author of the procedure into the standard format of SOPs.

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In conclusion, if procedures are correctly written, they will need little streamlining in the future, and will facilitate consolidation whenever new processes come on line and need to be captured in a procedure. Of course, if procedures have been poorly written, poorly chunked, or if there is a great deal of redundancy, then they must be revised along the lines sketched out above.

A fourth aspect of the fit between training modules and the larger curriculum is the relationship between training modules and the various regulatory requirements. That aspect will also be delineated in the Design phase.

5.2.3 How training modules relate to regulatory requirements

There are a number of regulatory regimes that impact on the training environment. These regimes include such agencies as FDA, OSHA, EPA, DOT, DEA, and others, each with its own set of regulations.[6]

On the one hand, the number of regimes means that there are simply more regulations to be taken into account. However, the various regimes can present the problem of regulatory overlap, where different agencies have differing regulations covering the same situation.[7] We will consider how this impacts the design of the training module.

First, it overlooks the very abnormality of the abend. After all, this is called an abend because, in important ways, it is abnormal. Second, it overlooks the distinct division of labor between operators who enact the routine steps of the manufacturing cycle and the mechanics who address the abnormal events. This has substantial training implications; the procedures tend to be much longer, and both groups must train on the whole GMP procedure. Third, it confounds the "operational" level of detail in the routine situations

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with the much more fine-grained level of detail in the abnormal situations, a level of detail that can only be addressed by reference to technical manuals. Fourth, it blurs regulatory requirements that differ between normal situations and exceptional situations, for example, OSHA safety regulations.

For these reasons, among others, it seems more appropriate to deal with abends by having separate procedures; an illustration will clarify this.

If we represent the manufacturing cycle in a vertical process map, displayed in Figure 5.6, consisting of the Set-up Period, followed by the Start-up Period, then the Operate Period, and finally the Shutdown Period, then abnormal events can be represented in a horizontal process map that intersects the manufacturing cycle at the point of the disruption. This horizontal map lays out the process of trouble-shooting,

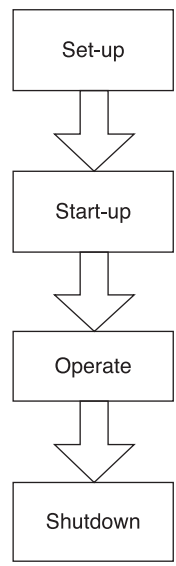

Figure 5.6 Manufacturing cycle

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reviewing service or maintenance instructions that are specific to the equipment, implementing a set of corrective and preventive actions, conducting follow-up monitoring, as well as addressing safety or other relevant regulatory concerns (Figure 5.7).

At the point of an abnormal event, the GMP requirements of the manufacturing cycle are suspended, temporarily, by an OSHA-mandated Lockout/Tagout (LOTO).[8] That is where the mechanics or engineers (in OSHA terms, the "LOTO Authorized employees") intervene with their Troubleshooting SOP and associated ESI to troubleshoot and maintain/repair the equipment.

These troubleshooting procedures and ESI protocols make up the horizontal process map. Its training modules would

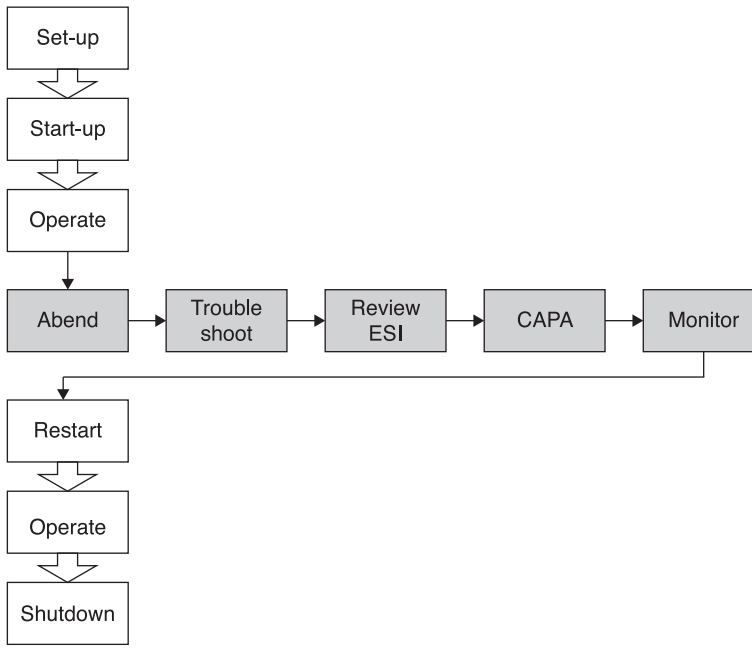

Figure 5.7 Manufacturing cycle with abend

look much the same as the template given above, where the Troubleshooting SOP would be delivered by an instructor in a classroom, or electronically; the ESI protocols would be SOJTs. These would appear on the curriculum of the mechanics, as shown in Figure 5.8.

After the abnormal event is under control, the LOTO is removed and the LOTO-affected employees (the operators) resume the manufacturing process again, under the guidance of the GMP procedures.

Back in the GMP realm again, and depending on the specifics of the abnormal event – for instance, the impact on the product – a Management Notification is prepared (a Notification of Event, NoE) that could lead to an investigation, corrective action and preventive action, and follow-up monitoring.[9]

By keeping these processes separated (vertical and horizontal), the operators would have training on the GMP procedures on their curricula, and would qualify on these modules. The mechanics would have training on the troubleshooting SOPs on their curricula, and would qualify on these modules. Thus the operators would not need to train on the troubleshooting modules and the mechanics

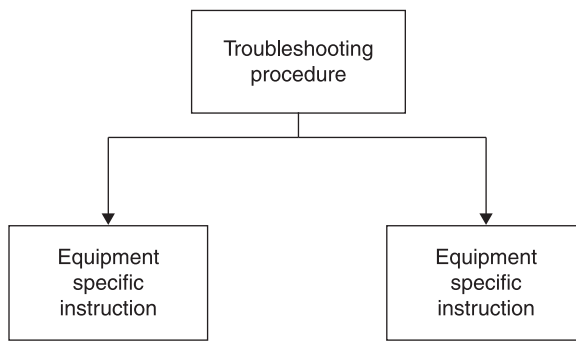

Figure 5.8 Training module for mechanics

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would not need to train on the operational modules. This would of course require that the SOPs would be written in a more focused fashion.

We have seen how the proposed training module is fitted into the larger curriculum in the Design phase of the program improvement model. The training module thereby aligns with other training module, and with organizational goals. We reviewed four aspects to this "fit:" the structure of training modules; the relationship between training module and SOP; how to reduce training time by consolidating SOPs; and the relationship between training module and various regulatory requirements.

Now we will consider how the proposed training module is outlined in the Design phase.

5.3 Outlining the proposed training module

Outlining the proposed training module will usually consist of completing a Training Outline template; the content of this is illustrated in Table 5.2. We will first display an illustrative template, with 12 fields and instructions for completing each field. This will be followed by comments on several of the fields.

5.3.1 Training audience

The personnel included in the module's training audience must be negotiated. Many times a training module will impact not only the business unit of the business owner of the SOP, but other units as well. Personnel in those impacted units will be listed on the Scope Statement of the SOP, and

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Table 5.2 Training outline content

FIELDS	INSTRUCTIONS
1. COURSE TITLE:	Enter the title of the document or course
2. COURSE NUMBER and VERSION:	Enter the number and version of the procedure, protocol, or document
3. TRAINING AUDIENCE	Those required job positions included in the scope of the training module. Identify the areas, departments, and positions. For example, a training audience may consist of: ■ all managers in a department ■ all managers and supervisors in an area ■ all employees in a department ■ all employees who operate the bottler on Packaging Line 84
4. CURRICULUM FIT	Identify the training module; other associated courses
5. PREREQUISITE COURSES/ REQUIRED SKILLS	List any prerequisite courses; any required skills
6. TRAINERS:	All qualified trainers who have been identified as SMEs on the course, including the Originator and Business Owner, if they are qualified trainers
7. BEHAVIORAL OBJECTIVES:	Specify the observable competencies that trainees will demonstrate upon completing the training. For example, "At the end of this training session, the trainee will be able to demonstrate the following skills or perform the following tasks . . ."
8. TRAINING DELIVERY METHOD:	Check as appropriate: ■ classroom ■ Structured On-the-Job Training ■ Computer-based training, etc.
9. COURSE LENGTH:	Enter the approximate time required to deliver the training session. This information is for planning purposes only.

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10. SPECIAL INSTRUCTIONS:	Instructions to facilitate the preparation and execution of the event (e.g., safety issues, logistical requirements, pre-work, handouts, etc.)
11. MEASURES of EFFECTIVENESS:	The KTA (and answer sheet) or SDA should be attached. The content of the KTA or SDA is derived from the Behavioral Objectives.
12. APPROVAL:	Includes dated signatures from: ■ Originator ■ Department Management and/or Business Owner ■ Quality Unit

also in the list of Task Responsibilities within the SOP itself. Unfortunately, these two lists of personnel do not always coincide.

Precisely defining the training audience becomes critical because those are the personnel who must be trained on the training module associated with the new or revised SOP. After a new or revised SOP has been approved, there is a "training window" before the procedure goes into effect, within which the impacted personnel can be trained on the SOP. This window is typically a week or two in length. It is critical that the training audience be defined before that window opens – before the SOP is approved – so that all the training will be completed before the effective date. Thus the risk of untrained personnel "touching" the regulated product will be minimized.

When the training module is in the Design phase, the author of the module can provisionally prepare a Target Audience List based on a review of the SOP Scope Statement as well as the Task Responsibilities. When the Training Outline is circulated for approval, the Target Audience List

can be circulated as well. Management of each impacted unit reviews the list and recommends limiting it or expanding it, based on their direct responsibility for the task assignments of the impacted personnel. The author of the training module can then take those recommendations into account as the module is finalized. Moreover, management in the impacted areas is alerted for the approval and implementation dates of the SOP, and can accordingly schedule personnel for necessary training. This topic will be discussed further in Chapter 13.

As an additional comment, it is important to recognize the different kinds of personnel that may be included in the training audience for a given SOP: (a) employees (in the strict sense), (b) independent contractors, (c) contract company (third-party) workers, and (d) temporary agency workers.[10] These four kinds are cross-cut by several kinds of ranks: (α) subordinates, (β) supervisors (i.e., managers, directors, etc.), and (χ) executives. The finalized Target Audience List must identify impacted (and non-impacted) personnel from each of these groups.

5.3.2 Behavioral objectives

There is a strong case to be made for behavioral objectives, sometimes called S.M.A.R.T. objectives, in training.[11] Moreover, behavioral objectives permit the alignment of the intended training outcomes with organizational objectives. Anyone who advocates cognitive (i.e., non-behavioral) objectives for training must be prepared to explain how these objectives are to be aligned with those of the organization. Also, behavioral objectives permit the trainee to have clear expectations of the trainer's (and the organization's) intended training outcomes.[12] These clear expectations play a critical role in effective adult learning.

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Many academics reject the role of behavioral objectives in the university classroom; this highlights the difference between training in industry, on the one hand, and higher education on the other. In higher education, accredited institutions award diplomas to students, on the basis of a series of learning experiences over an extended period of time. The organizational objectives include (a) awarding the diplomas, and (b) maintaining the accreditation. This has very little to do with training in industry, where the organizational objectives include (a) improving employees' task performance on-the-job, and (b) addressing the requirements of various regulatory regimes.[13]

5.3.3 Training effectiveness

Assessment of training effectiveness must be distinguished from evaluation of training programs. There is a difference in kind – trainees are human individuals, training programs are organizational entities. Of course trainees participate in training programs, but the difference in kind means that the measures are different. For instance, trainee reactions (Donald Kirkpatrick's Level One)[14] are perhaps useful in evaluating training programs – favorable trainee reactions may weigh in decisions about program continuity. Trainee reactions are much less useful in assessing training effectiveness, which involves assessing performance improvement that will impact on-the-job – a supervisor's reactions are much more relevant.[15]

In the present context, training effectiveness is assessed by one of two types of measures – a KTA or a SDA. The KTA in particular need not be validated in terms of the task(s) at hand. If the KTA is validated, then performance improvement on-the-job can be predicted from trainee performance on the KTA. If the KTA has not been validated, the measure can still

be included in the training module, as an interactive element of the courseware, and as a promissory note of future validation. The training event will be concluded in this case by the trainee (and trainer) concurrence that the trainee was trained on this courseware, and thereby on the SOP.

An SDA, by contrast, directly and validly documents the trainee's ability independently to perform the task(s). Furthermore, once the relevant SDAs for a process are completed, the trainee is qualified, able independently to perform the tasks in that process. These matters are discussed further in Chapter 9.

Once the template is completed by the author, it is ready for management signoff, which concludes the Design phase of the program improvement model.

5.3.4 Securing management approval of the outlined training module

The final component of the Design phase is management approval of the proposed training module. This approval is important for at least three reasons. First, this ensures that resources allocated to the subsequent phases, Development, Implementation, and Evaluation, have approval at the appropriate organizational level. The investment of resources – particularly in the Development phase – will be substantial, and knowledge workers, be they program developers, instructional designers, software engineers, or whomever, are in no position to make the management decision about resource allocation. Second, Quality Unit approval ensures that the proposed training module meets the organization's quality criteria. Finally, there are a number of points where training implications of the proposed module – the training audience, the course length, etc. – can have a profound impact on business lines, and again, this impact must have

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managerial approval. The signatures on the Training Outline satisfy these needs.

5.4 Conclusion

The Design phase of the program improvement model is the occasion for a carefully planned approach to addressing a problem or performance gap identified in the Analysis phase. This planned approach includes fitting the proposed program into the larger programmatic framework; it involves outlining the program in terms of a systematic template, the Training Program Outline; and it includes the need for securing management approval of the outlined program.

When the proposed program has moved through the Design phase, it is ready for the Development phase where training materials and assessment materials are developed to address the problem or performance gap.

5.5 Notes

1. See Sanne Dijkstra and Henny Leemkuil (2008).
2. See D. Zielinski's (2005) discussion of "blended learning models." See also Harvey Singh (2003). As B. Hall and J. LeCavalier (2000) put it: "Across a range of industries, the emerging best practices model is a highly compatible 'ménage à trois' uniting online learning for information transfer and procedural skill acquisition (often this constitutes pre-work for the next tier of the model), classroom or other site-based learning for higher order competencies, and SOJT learning, integrated with knowledge management and competency evaluation."

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3. On SOJT, see William Rothwell and H C Kazanas (2004); also Ronald L Jacobs (2003).
4. See 21 CFR Part ∫211.25, "Personnel qualifications."
5. See 21 CFR Part ∫211.28, "Personnel responsibilities." Also Jan Eudy (2004).
6. See, for example, Lawrence Bierlein (1998); also Bierlein (2005); and Shadid Jamil, H.L. Floyd, and D. Pace (1999). There are also state laws and regulations that must be taken into account; see A. Bender, N. Shannon, and J. Braun-Davis (2005).
7. For instance, the chain of custody required by DEA 21 CFR Part ∫1301.73, "Physical Security Controls . . ." and the evacuation requirements of OSHA 29 CFR ∫1910.38(c), "Emergency Action Plans." See also National Academy of Sciences/ Institute of Medicine (1998). See Society of the Plastics Industry (1998):

   > over the years, the food packaging industry has been subjected to an undue burden as a result of the regulatory overlap among FDA, USDA, and the Bureau of Alcohol, Tobacco, and Firearms (BATF);

   and "FDA Cancels Part 11 Meeting," *Part 11 Compliance Report* (9 June 2004), Vol. 4, No. 12, p. 2, for a discussion of the regulatory overlap between 21 CFR Part 11 and other regulations affecting life science companies, such as HIPAA and Sarbanes-Oxley. For an overview, see Robert W. Hahn (1988).
8. See 29 CFR ∫1910.147, "Control of hazardous energy." This standard mandates that each workplace, with few exceptions, must develop a program to "disable machinery or equipment and prevent the release of potentially hazardous energy while maintenance and servicing are being performed." Hazardous energy includes electrical, mechanical, hydraulic, pneumatic,

and other energy sources. The mandated LOTO program will have three components:

1. a set of written procedures for the control of hazardous energy;
2. an employee training program to ensure that the procedures are implemented; and
3. an annual inspection to ensure that the procedures continue to be followed.

See also *Federal Register* (6 November 1989), Vol. 54, No. 213, p. 46610; and Danny P. Liggett (2005).

9. The corrective and preventive actions (CAPA) may, in the event, be the same for the troubleshooting process and the manufacturing process.
10. See John Garen (2006).
11. See D.D. Ely (1975).
12. As Craig Cochran (2004) has stated, "People have trouble contributing to fuzzy, undefined objectives."
13. As Harry Moser (2005) points out, higher education is not incompatible with training in industry – just different. See also E.J. Rice-Munro and R.A. Munro (2004).
14. See Donald Kirkpatrick (1994); also James Kirkpatrick (2005).
15. See R.K. Mahapatra and V. Lai (2005).

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6

Content development: a new employee orientation program

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Abstract: This chapter addresses the development of a new employee orientation (NEO) program for GXP compliance. There are two major sets of organizational expectations for the workplace performance of a new employee – compliance and productivity expectations. These expectations are operative from the new hire's first moment on the job, hence NEO is a timely setting for presenting these expectations. This chapter reviews the Employment Life-cycle, the comprehensive process every employee goes through from recruitment to separation, and situates NEO in that life-cycle. Next, various features of a typical NEO program are sketched. Then a scenario-based discussion of regulatory overlap is presented, as well as appropriate employee responses. This is followed by an episodic approach to the history of the FDA. These episodes are employed as illustrations of the process of continuous improvement (i.e., identification of problems (deviations), investigation and root cause analysis, and remediations). Finally, several aspects of the organization of the NEO program are presented, including the necessity to coordinate the program across several departments.

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Key words: elixir sulfanilamide, Employment Life-cycle, FDA (history of), management notification, new employee orientation (NEO), regulatory overlap, *Salmonella* contamination, Upton Sinclair's *The Jungle*, thalidomide, tylenol poisoning.

6.1 Introduction

The new employee orientation (NEO) program can importantly contribute to both GXP compliance and organizational productivity. NEO can contribute to GXP compliance by indicating to the new hire or transfer that the organization (and the regulatory agency) has a series of expectations for employee performance in the workplace. These expectations:

- are covered by the GXP regulations, corporate policies, and local procedures;
- are written and readily available to employees; and
- are mandatory.

The new hire or transferred employee may not have experienced such regulation in his or her previous position.

The NEO program can contribute to organizational productivity by presenting new hires with the organization's process for assessing workplace performance, such as employee productivity. The organization's expectations are summarized in the specifics and criteria of the periodic performance review process. Again, new hires or transfers may not have experience with such processes, and can adjust their performance to meet the expectations.

However, both sets of expectations for workplace performance – compliance and productivity – are operative

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from the new hire's first moment on the job. Thus the NEO program is a timely setting for presenting these expectations. However, both sets of expectations are far too extensive to present in detail in the time available for NEO. The question becomes: How to decide what to cover in the NEO program?

As a preliminary point, the term "new employee" should briefly be analyzed. The term is ambiguous – as Rollag points out, "everyone might agree that an arriving recruit is a 'new employee' on the first day [but] when do members stop being considered as 'new employees?'"[1] Likewise, the new employee is frequently mentioned in discussions of "onboarding," even though "The most successful onboarding programs [. . .] last one to two years."[2] This ambiguity may have an impact on the scheduling of NEO programs, for example those that are scheduled on a biweekly or even monthly basis. Thus the new employee can be on the job for days or weeks before participating in the NEO program. It will become clear that such scheduling practices can present serious GXP compliance issues, or else prevent the new hire from being assigned to work in a controlled (limited access) area.

6.2 NEO and the Employment Life-cycle

NEO is a crucial element in the Employment Life-cycle. This section presents an overview of the Employment Life-cycle and its components, including NEO, and two of the perspectives from which that cycle can be viewed – the organizational viewpoint and the viewpoint of the individual employee. Next, the contribution that participating in the NEO program can make for organizational and employee goals is considered. Finally, this section discusses the

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Table 6.1 Employment life-cycle

■ Advertising the position
■ Recruiting
■ Selection
■ Hiring
■ New Employee Orientation (NEO)
■ Probation
■ Training and Development
■ Performance Review
■ Promotion
■ Coaching and Disciplining
■ Separation
■ Benefit Entitlements

relationship between the overall process of employee socialization and the NEO program.

The Employment Life-cycle can be defined in terms of the following 12 elements: advertising the position, recruiting, selection, hiring, NEO, probation, training and development, performance review, promotion, coaching and disciplining, separation, and benefit entitlements (Table 6.1). This chapter focuses on NEO, its importance, and its impact on subsequent elements.

6.2.1 Perspectives on the Employment Life-cycle

This life-cycle can be viewed from either the individual employee's perspective or the organization's perspective. However, there are differences between these two perspectives. For example, advertising a position will look different from the organizational viewpoint versus the employee viewpoint.

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From the organization's viewpoint, the job posting will have content that is determined by a review of unit needs and resources; for instance, the position may require a BSc in Chemistry and five to seven years experience in FDA-regulated industry. From the individual employees' viewpoints, internal candidates may view the posting earlier than external candidates, may see the name and position of the hiring manager, etc. For another example of differences, from the individual employee's viewpoint, separation will mean different things in terms of benefits if the employee transfers, retires, or is terminated for cause. From the organization's viewpoint, the same separation will implicate issues of business continuity and succession planning, whether it is due to transfer, retirement, or termination.

However, there are similarities between the individual employee's and the organization's perspectives. In particular, reaching the first performance review is obviously important for the employee, especially if that review is positive. Similarly, it is important for the organization since it validates the resources expended in advertising the position, recruiting, and interviewing those persons in the applicant pool, and then selecting and hiring the particular employee whose initial performance review will prove to be positive.

6.2.2 Objective of the NEO program

Regardless of the differences of perspective, it is important for both the organization and the individual employee that their views come to be aligned, to whatever extent possible. A well-focused NEO program can contribute to that goal. A NEO program seeks to engage new hires or transferred employees more rapidly with the organization. It seeks to ensure that their behavior aligns more rapidly with the organization's culture and expectations for the workplace.

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Such a program intends to lengthen employees' tenure at the organization, as well as their motivation to perform successfully in the new position.

The NEO program is thus a specific, programmatic component in the overall process of socializing the employee to fit into the organization. It is limited in time, occurring within the first few days of hiring or transfer, in contrast to:

- onboarding, which occurs over months or even years; or
- the process of employee socialization that takes place throughout the entire Employment Life-cycle.

NEO is a program, with a more or less well-defined set of participants and agenda, in contrast to the disparate set of formal and informal activities and interactions that comprise onboarding or employee socialization in general.[3]

This section has discussed the place the NEO program holds in the Employee Life-cycle. In the next section, a typical NEO program will be sketched, highlighting elements of the program that address regulatory issues and, in particular, GXP regulations.

6.3 A typical NEO program

A typical NEO program includes several elements:

- a welcome and mission statement from an officer of the organization;
- presentation(s) on expectations for the workplace;
- a presentation on organizational structure, history, and culture;
- a series of transactions facilitated by a representative of Human Resources (HR), based on resources (whether

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available on-line or in a binder) containing information about employee benefits, beneficiaries, HR policies, confidentiality agreement, and standards of business conduct.[4]

Moreover, in regulated industry, the NEO program can include regulatory elements, for example, safety and GXP topics.

The NEO program is an appropriate occasion to present material that immediately impacts most or all employees. Thus an official greeting, as well as the organization's mission statement, structure, history, culture, and resources on employee benefits, are relevant to all employees. For example, the mission statement could include the following:

"An organization in FDA-regulated industry is responsible for products that can directly affect customers' health and quality of life. Product failure could result in death or sickness. Working for an organization where products help preserve and sustain life comes with the responsibility to know one's job and perform it correctly at all times."

An official greeting can contribute substantially to a new hire's integration into the workplace as well as to an organization's success. As an illustration, Don Mayne, the Company Executive Officer (CEO) of Dorothy Lane Markets in Dayton, OH, has personally greeted every new employee for the past 20 years. He wants all the company's new hires to understand the company's culture, customers, and competitors. And Dorothy Lane Markets has margins twice as high as the industry average.[5]

Content that does not immediately impact the new hire, or only impacts new hires in several departments or units, is better deferred until departmental or unit training activities. More generally, material that is task specific tends to be appropriate for technical training at the departmental or unit

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level, while content that is domain (or context) specific tends to be appropriate for the NEO program and other, subsequent regulatory training.[6] Thus the GMP regulations stipulate that "training shall be in the particular operations that the employee performs," which is to say technical training that tends to be more task specific. The regulations go on to say that training shall also be "in current good manufacturing practice (including cGMP regulations in this chapter and written procedures required by these regulations)," which is to say regulatory training that tends to be more domain specific.[7]

Let us consider several examples of domain specific content. The first illustrations involve Occupational Safety and Health Administration (OSHA) regulations. In any industry, a presentation of workplace expectations will include a review of environmental, health, and safety (EHS) issues that directly impact employees. This review will ensure, for example, that all employees can respond appropriately to various industrial safety warnings and alarms that may be encountered from their first moment on the site.[8] By way of illustration, OSHA regulations stipulate that: "Employers shall provide employees with effective information and training on hazardous chemicals in their work area at the time of their initial assignment."[9] Because of the immediate need new employees have for this information, the NEO program is a good occasion to present it.[10]

As another example, employees must have immediate and continuing access to Material Safety Data Sheets (MSDS). The significance of the MSDS for employee safety can be covered in the NEO program; the process of accessing this information can be addressed as well. Should the organization use an electronic document management system (EDMS) to capture the MSDS, this portion of the NEO program can be

conducted in a networked computer classroom, where the new employees can be stepped through the process of logging on to the organization's intranet, accessing the EDMS, and retrieving a MSDS. The presentation of employee safety issues in a NEO program is typically facilitated by a representative of the EHS unit.

In FDA-regulated industry, another presentation of workplace expectations will include a review of relevant GXP regulations to ensure that the employee will be compliant in each assigned task according to regulations, corporate policies, and local procedures. Again, these compliance issues may arise from the first moment the employee is on the site. This GXP review will ensure, for instance, that the new employee is "instructed to report to supervisory personnel any health conditions that may have an adverse effect on drug products."[11]

An important topic that should be covered in the GXP review is the FDA requirement that employees have immediate and continuing access to relevant SOPs. Good laboratory practice (GLP) regulations, for instance, stipulate that "each laboratory area shall have immediately available laboratory manuals and standard operating procedures relative to the laboratory procedures being performed."[12] Because new employees may have an immediate need to access procedures, the NEO program is a timely occasion to address this issue.

For example, a newly hired Animal Care Technician must have immediate access to the lab's procedures for the identification of test animals. The process of accessing this information can be addressed in the NEO program.[13] If the lab makes the SOPs available in an EDMS, this part of the GLP review can be conducted in a networked computer classroom, where the technician can go through the process of logging on to the organization's intranet, accessing the

EDMS, and retrieving the relevant SOP. Access to this material is typically facilitated by PharmOps staff.

In addition to the OSHA and FDA regulatory areas, other corporate policies addressing workplace expectations – topics such as security, intellectual property rights, and corporate intranet access – must be presented.

This section sketched out a typical NEO program, highlighting program elements that address regulatory issues and, in particular, GXP regulations. The next section will discuss regulatory overlap, and suggest ways this can be addressed in a NEO program.

6.4 Regulatory overlap and its implications

Another important topic that should be covered in the NEO program is the complexity of regulatory regimes and regulations that impact the organization, as well as the individual employees. These regimes include such agencies as the FDA, DEA, DOT, EPA, OSHA, and others, each with its own set of regulations. As already noted, the new hire or transferred employee may have an employment background that was not subject to regulation by some of these agencies, or to such complexity of regulation.

On the one hand, the sheer number of these disparate regulations means that they cannot be considered in any detail in the NEO program. They will need to be addressed, on a timely but "as needed" basis, during training subsequent to NEO. However, the various regimes can present the problem of regulatory overlap, where different agencies have differing regulations covering the same situation. This complexity can be raised during NEO, and several ways the affected employee can appropriately respond can be highlighted.

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Consider, as an illustrative example, the following scenario and guided discussion, which can be incorporated into a NEO session. It has three parts. The first part is the presentation of the scenario and an invitation to the new hires to share their responses to it. The second part is a facilitated discussion of the way SOPs provide guidance for most situations the new hires will confront in the workplace. The third part presents the principles that control the situation when procedures do not suffice. This allows the NEO program to comfortably introduce new hires to issues of regulatory complexity, appropriate and inappropriate ways to respond to that complexity, the role of SOPs in regulated industry, and the necessity of problem escalation and change control when the current procedures are clearly inadequate. Here is the scenario:

> A couple of newly hired employees, call them Francine and Frank, have been duly screened and certified for work with a controlled substance. During their first hour on the job, while processing the controlled substance, the fire alarm sounds in their area.

Ask the participants in the NEO session: How should Francine and Frank respond? Points to raise include the following:

> On the one hand, the chain of custody required by the Drug Enforcement Agency stipulates that "manufacturing activities with controlled substances shall be conducted in an area or areas of clearly defined limited access which is under surveillance by an employee or employees designated in writing as responsible for the area.[14]

However, evacuation requirements of the OSHA call for "procedures for emergency evacuation, including type of evacuation and exit route assignments."[15]

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Do Francine and Frank remain in the limited access area and maintain the chain of custody for the controlled substance, complying with DEA regulations. Or do they immediately evacuate the area with all due speed, complying with OSHA regulations?

When this scenario is presented to line personnel in a NEO session, the responses vary widely. Many participants simply say "Francine and Frank should get out quickly." Some say "They should use their good sense." Others say "They should ask Joe," or "Follow Joe," Joe being a fellow worker in the controlled substances area, a 20-year veteran employee, a sea lawyer.

Some participants point out that in the case of a fire, or even a fire alarm, a Notice of Event (NoE) will be required, so evacuating – breaking the chain of custody for the controlled substance – will be covered by the NoE anyhow. A few suggest that the relevant SOPs should be consulted – presumably in advance of the fire alarm.

It is important in the NEO session for the facilitator to point out that no known organization in regulated industry has a procedure that states "Use your good sense" or "Ask Joe." It is also important to explore further the point about a NoE. What does a "Notice of Event" mean? Since some of the new hires in the orientation session may not have employment experience in regulated industry, they may not know that this means that a deviation has occurred, a deviation that may involve non-compliance with a SOP. This will help focus the discussion of the scenario on the topic of relevant SOPs. Clearly the facilitator of this portion of the NEO session will have already reviewed the local procedures that address the issues brought out in the scenario.

When the discussion focuses on the role of written procedures, the point can be reinforced that the FDA requires employees have direct and continuing access to relevant

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SOPs. SOPs that cover such situations typically indicate that line personnel such as Francine and Frank should comply with the emergency evacuation plan for the area. But the procedures go on to say that their supervisor is responsible for maintaining the chain of custody for the controlled substance. This seems to accord with the stipulation in ∫1301.73(b) that an employee, "specifically authorized in writing," shall be responsible for the area.

Of course this does not resolve the question initially posed: How should Francine and Frank respond to the scenario? It simply shifts the question from all employees certified for work with controlled substances to their supervisors. The employees, including Francine and Frank, can evacuate – but what about the supervisors? Do they remain and maintain the chain of custody for the controlled substance, complying with DEA regulations, or do they too evacuate the area, complying with OSHA regulations?

If the relevant SOPs do not provide guidance for the fate of the supervisors, this helps to further focus the discussion on the topics of problem escalation and change control in regulated industry. Once it is evident that there is no SOP that covers the supervisors in the scenario, and once the inadequate answers "Ask Joe," "Use good sense," have been dispensed with, the participants can be introduced to the principles that control the situation. Two important principles are Management Notification and Change Control:

> Most organizations have the following workplace expectation: Employees shall escalate any problem that they do not know how to deal with, to their supervisor.

This escalation process can be proceduralized; call the SOP "Alert Management, Notification, and Escalation." This

procedure can be referred to and summarized at this point in the NEO session:

> Moreover, organizations have another workplace expectation: Employees shall deal with unexpected situations in an orderly fashion – situations for which currently implemented SOPs do not provide guidance, or SOPs that are clearly inappropriate.

This expectation that change will be controlled is captured in the organization's "Change Control" procedure. This procedure also can be referenced and summarized at this point.

Overall, discussion of this scenario in the NEO session should give new hires the following takeaway:

> The web of regulations is complex, but distinct processes and procedures are operative even in the most complex situation.

At this point, having presented the scenario and discussed topics of the complexity of regulations, appropriate and inappropriate responses to that complexity, the role of procedures, and the necessity of problem escalation and change control when the current procedures are clearly inappropriate, the agenda can move to broader areas of organizational history and culture.

6.5 Presenting the history of the FDA

In regulated industry, the history of the FDA is usually presented in a NEO program as part of organizational culture and history. The historical account might be

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Table 6.2 **Critical episodes in the history of the FDA**

■ Upton Sinclair's *The Jungle*	1906
■ Elixir Sulfanilamide	1937
■ Thalidomide	1960s
■ Tylenol tampering	1982
■ *Salmonella* contamination	2000s

summarized in four or five critical episodes, including the origin of federal regulations, the development of drug safety regulations, and other episodes (Table 6.2). Several threads can be drawn from these illustrative episodes, and presented in the NEO program.

The first thread discusses public concern and official responses to these crises – legislative responses such as the Food, Drug and Cosmetic Act of 1938, as well as regulative responses such as 21 CFR 58 and ʃ211. That thread provides an opportunity to summarize the history of the FDA for the new employees.

As an important episode in the origin of federal regulation, take Upton Sinclair's book *The Jungle*. It was based on Sinclair's own investigative journalism in late 1904 in the Chicago stockyards and meatpacking industry. This book was serialized in the journal *Appeal to Reason* in early 1905, and was published by Doubleday in early 1906. It graphically recounted the plight of workers and the adulteration of food that characterized the meatpacking industry. This book dramatically disclosed the problems in the industry, and its publication and popularity contributed to the signing of the Pure Food and Drugs Act in June 1906.[16]

The book is a crucial factor in the emergence of the 1906 legislation. It should be stressed that there had been widespread concern about adulterated food and drugs in the

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United States even before 1904. President Theodore Roosevelt had called for legislation to regulate "misbranded and adulterated foods, drinks, and drugs" in his State of the Union statement in late 1905. Many factors combined to lead to the passage and signing of the legislation, including Sinclair's book.[17]

This was also the case with the Elixir Sulfanilamide disaster of 1937, which was a critical episode in the emergence of drug safety regulations. When the sulfa drugs first came to market, they were distributed in tablet form. Soon, the S.E. Massengill Company developed a liquid preparation. This was the Elixir Sulfanilamide, with diethylene glycol (DEG), water, and sulfanilamide as the main ingredients. The solvent, DEG, was not listed as an ingredient, nor were existing animal studies of the solvent consulted. The Elixir was distributed across the United States in late 1937, and resulted in over 100 deaths due to DEG poisoning.[18]

This tragedy contributed to the introduction of a bill that eventuated in the Food, Drug and Cosmetic Act, signed into law in June 1938. Among other provisions, it required that a new drug application (NDA) provide evidence of drug safety. As FDA Commissioner Walter G. Campbell had argued in October 1937:

> In the interest of safety, society has required that physicians be licensed to practice the healing art. Pharmacists are licensed to compound drugs. [. . .] Certainly a requirement that potent proprietary medicines be manufactured under license can be justified on the ground of public safety.[19]

Once again, many factors – including the tragedy itself – combined to lead to the passage and signing of the legislation.[20]

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Another episode involves thalidomide, which was manufactured and marketed in Europe by Chemie Grünenthal of (West) Germany as a tranquilizer in the late 1950s, and was used to relieve morning sickness. Soon thalidomide was associated with peripheral neuritis. A letter from Dr Leslie Florence to the *British Medical Journal* suggested that "these symptoms could possibly be a toxic effect of thalidomide."[21] Next, a letter from Dr W.G. McBride was published in *The Lancet* suggesting that thalidomide, when used for morning sickness by pregnant women, was accompanied by a pattern of severe birth defects.[22] Finally, thalidomide was withdrawn from the West German market because of safety concerns. Thalidomide was not commercially distributed in the United States during this episode, although it was distributed for clinical trials.[23]

As a consequence of the thalidomide tragedy, the Kefauver–Harris drug amendments to the Food, Drug, and Cosmetic Act were signed by President John F. Kennedy on 10 October 1962. These regulations mandated an Investigational New Drug Application (IND) for the trials. Moreover, the regulations include informed consent of subjects of clinical trials, qualified investigators to conduct the trials, Institutional Review Board (IRB) approval of changes to a study protocol, and reporting of adverse events (AEs).[24]

Further episodes might include Tylenol tampering (1980) and, if there is a desire to highlight current events, *Salmonella* contamination (1990s; today).

A second thread immediately follows the historical summary. This thread treats each of the episodes as the occasion for continuous improvement – problem identification, investigation, root cause analysis (RCA), and remediation through corrective action and preventive action. That thread can familiarize the new employees with regulated industry's approach to continuous improvement and risk

management. The episodes illustrate this continuous improvement through the logic of investigation and remediation.

To return to the several episodes mentioned before, *The Jungle* can represent the issue of problem identification and triage. What is the evidence for a problem, and how important is it? What is the risk, what is the severity associated with the problem? When Sinclair's book was published, there was substantial dispute in the press about the accuracy of his account.[25] President Roosevelt sent Charles P. Neill and James Bronson Reynolds to Chicago to ascertain and report the truth of the book's claims. Roosevelt delayed releasing their report, which basically substantiated Sinclair's claims. As Sinclair expressed it about the meatpacking industry, "The packers worked on the President's sympathy [. . .] in order to keep the true conditions from the public." Sinclair went on to insist that the Neill–Reynolds report be made public.[26] The report was finally made public and contributed to the signing of the Pure Food and Drugs Act in June 1906.[27]

The Elixir Sulfanilamide poisoning episode can represent the issue of investigation and RCA. What factors might have contributed to a problem, and which is most likely the fundamental, or root cause? A few days after 11 October 1937, when the first cases of poisoning were reported from Tulsa, OK, the American Medical Association (AMA) had begun to investigate and suggested that it was the solvent, DEG, that was the cause.[28] S.E. Massengill, the company that had manufactured and distributed the Elixir, continued to argue that the solvent was not the cause, that the poisoning was the result of interaction of the Elixir with other drugs.[29] By carefully identifying the potential factors – the active ingredient, the solvent, the other excipients, and other factors ("other drugs"), then weighing their actual effects, the chemists were able to identify the root cause, the toxicity of

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ethylene glycol. As a byproduct of the RCA, Samuel Massengill himself was charged with mislabeling and misbranding the Elixir and fined $26 000.[30]

The thalidomide tragedy can be considered an example of corrective action. In (West) Germany, a pediatrician named Widukind Lenz began to suspect that thalidomide was associated with a dramatic increase in birth defects. Lenz presented his findings at a medical conference in 1961. This account was picked up by a widely read newspaper, *Welt am Sonntag* (26 November 1961), which called for the withdrawal of the drug. Under pressure from (West) German government officials, while still contesting the findings, Chemie Grünenthal withdrew thalidomide from the German market a few days later. Further evidence accumulated and the public outcry increased. This lead to criminal indictments filed in 1967 against Chemie Grünenthal officials. The trial lasted three years. It finally ended when the company agreed to establish a substantial fund to provide for the victims of thalidomide, and the defendants were released from further liability.[31] This is an example of a corrective action, where steps are taken (establishing the fund for the victims) to in part remedy the problem (the administration of a dangerous drug during pregnancy).

The heroic role of a FDA medical officer, Frances Kelsey, to prevent thalidomide marketing in the United States represents a somewhat more oblique instance of corrective action. When Wm. Merrill Co. submitted a NDA for thalidomide to the FDA on 12 September 1960, the documentation included evidence of drug safety based on the distribution of the drug in Europe. Frances Kelsey and her colleagues at the FDA noted omissions in the application. Merrill responded to requests for further evidence. As Kelsey continued to delay approving the application, awaiting further safety evidence, Merrill became increasingly

impatient. Finally, Dr Kelsey corrected the misperception of responsibilities that had crept into the situation.

> In the consideration of an application for a new drug, the burden of proof that the drug causes side-effects does not lie with the FDA. The burden of proof that the drug is safe – which must include adequate studies of all manifestations of toxicity which medical or clinical experience suggest – lies with the applicant.[32]

While this corrective action does not focus on the victims of the unsafe drug, it does focus on the locus of responsibility for evidence regarding drug safety.

The Tylenol tampering case can be considered an example of preventive action. What steps can be taken to prevent the recurrence of a problem? In 1982, Tylenol was the nation's leading non-prescription painkiller. In late 1982, a number of persons in the Chicago suburbs died from cyanide poisoning after swallowing Extra-Strength Tylenol in capsule form.[33] It was quickly determined that the capsules had been opened somewhere along the distribution chain, possibly in the retail outlet, and the cyanide was added. The capsules were then reassembled and sold by the unsuspecting retailer to the unsuspecting consumer. Within a month, the pharmaceutical industry had asked the FDA to develop regulations for tamper evident packages.[34] The FDA prepared new regulations requiring tamper evident packaging which went into effect in early 1983.[35] While the preventive action seems to have been reasonably effective, there has never been a criminal conviction in the case.[36]

Finally, the current episodes of *Salmonella* contamination could represent the need for robust maintenance and diligent implementation of the system of investigation and remediation. The contamination of peanuts has taken

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8 lives and sickened some 19 000 people in more than 40 states.[37]

This section has sketched an historical account of the FDA that can be presented in the NEO program. The sketch limits itself to four or five critical episodes. Several threads were drawn from these illustrative episodes. One thread provided an opportunity to summarize the history of the FDA for the new employees. Another thread treated each of the episodes as representing the logic of investigation and remediation. That thread was intended to familiarize the new employees with regulated industry's approach to continuous improvement and risk management. The following section will touch on aspects of the organization of the NEO program, including the need for coordination.

6.6 Organizational issues

The breadth of topics that must be covered in a NEO program means that there must be close coordination and buy-in of each department that is involved. This usually includes HR, EHS, and the GMP training unit, as well as other units. A representative of each of these units should be a member of a coordinating committee for the whole program. This committee should work closely with the business owner of the NEO program, whether that business owner is located in HR or some other department. In addition, if senior management is to be involved in welcoming new hires, that activity must also be closely coordinated. It may also require coaching the officer in this role, as some are good at it and others are not.

The high visibility of the NEO program means that all facilitators must be fully engaged in their assignments. None of the facilitators can behave as though they feel that their time would be better spent elsewhere. Nor can the facilitators

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behave as though they feel that they will never see the new hires again, once the sessions are completed, no matter how large the organization. Each facilitator must recognize the value of the program and be willing – even eager – to help welcome the new hires to the organization. These points about facilitator performance are important because they may be overlooked due to the cross-functional nature of the program. The coordinating committee should be responsible for reviewing not just program content but facilitator performance as well, to ensure these contents and performances are aligned with organizational goals.

Because of the breadth of topics addressed in a NEO program, the multiplicity of departments involved, and the crucial need to convey the information in a timely fashion, the NEO program should be proceduralized. This SOP can be developed from several sources, including:

- the charter for the coordinating committee;
- the various subject matter experts involved from the several departments; and
- the agenda for the NEO program that has been approved by the various departments, with all the times, facilities, materials, and responsibilities clearly delineated.

6.7 Conclusion

This chapter has addressed several issues that emerge in the development of a NEO program for GXP compliance. NEO is a critical step that a new hire or transferred employee takes in an organization. This is a step in the path to reach his or her first performance review. The path itself is an early segment of the employment life-cycle, the comprehensive process every employee goes through from recruitment to

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separation. This chapter reviewed the Employee Life-cycle, and various features of a typical NEO program were treated. A scenario-based discussion of regulatory overlap was presented, as well as appropriate employee responses. This was followed by an episodic approach to the history of the FDA. These episodes were employed as illustrations of the process of continuous improvement (i.e., identification of problems (deviations), investigation and RCA, and remediations). Finally, several aspects of the organization of the NEO program were presented, including the necessity to coordinate the program across several departments.

6.8 Notes

1. See Keith Rollag (2007).
2. See B. M. T. (2008).
3. John P. Wanous and Arnon E. Reichers (2000). For further discussions of NEO programs, see Doris Sims (2001) and Karen Lawson (2002).
4. For checklists of topics included under resources and information, see Kathryn Tyler (1998) or David K. Lindo (1999). The new employee orientation program should not be restricted to these HR activities; as Garvey has pointed out, recent "NEO initiatives are getting more creative and comprehensive, and they are moving away from those painful sessions with stacks of HR forms and dusty videos." See Charlotte Garvey (2001).
5. Keith McFarland (2006).
6. Thus it is a GXP requirement that employees must be appropriately gowned for an assignment in a limited access area of the site, but gowning procedures may vary in terms of different limited access areas. For gowning in GMP sites, see 21 CFR 211.28(a), for

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gowning in GLP sites, see ∫58.29(e). Subsequent regulatory training includes "training in cGMP [that is conducted] on a continuing basis and with sufficient frequency to assure that employees remain familiar with cGMP requirements applicable to them;" 21 CFR 211.25(a). This implicates quarterly or annual cGMP refresher training, etc. as a follow-up to the GMP content in the NEO program.

7. 21 CFR 211.25(a), "Personnel Qualifications."
8. Audrie Armes (2006).
9. See Occupational Safety and Health Administration, 29 CFR 1910.1200(h)(1).
10. It is suggestive that Peter M. Smith and Cameron A. Mustard (2007) report that only one-fifth of Canadian employees received safety training during their first year of a new job; moreover, the provision of safety training does not seem to be more prevalent among workers or in occupations with increased risk of injuries. This included safety training during orientation.
11. CFR 211.28(d), "Personnel Responsibilities." Either the EHS presentation or the GXP presentation (or both) should make clear that the former presentation addresses the safety of the employee, while the latter addresses the safety of the product or the non-clinical lab materials.
12. 21 CFR 58.81(c), "Standard Operating Procedures." See also Organisation for Economic Co-operation and Development (OECD) (1997): "Each separate test facility unit or area should have immediately available current Standard Operating Procedures relevant to the activities being performed therein." As Jürg Seiler (2005) has put it:

> . . . the distribution of SOPs is on the one hand governed by the requirement that the relevant SOPs

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> should be immediately available at the workplace, and on the other hand, that work should be performed only according to approved and current SOPs.

13. The actual content of the SOPs will probably be better addressed in later training at the departmental or unit level.
14. 21 CFR Part 1301.73(b), "Security Requirements."
15. 29 CFR ∫1910.38(c), "Emergency Action Plans."
16. See Anthony Arthur (2006); see also Upton Sinclair (1962).
17. See Arlene F. Kantor (1976); see also James H. Young (1990). As Daniel Carpenter and Gisela Sin (2007) have aptly put it, Sinclair's book "eased the path for the Pure Food and Drugs Act of 1906." Scott Sutton points out that the *United States Pharmacopeia* (USP) was "recast from its traditional focus of how to make medicines to the role it would eventually take as a book that describes the safe making of medicines," in its eighth revision, in 1900. This provides further evidence that the regulatory climate was ready for the passage of the Act. See Sutton (2009).
18. See Paul M. Wax (1995). DEG is used as an antifreeze. See also Kirstin Jarrell (2012).
19. Quoted in Carpenter and Sin (2007), p. 168.
20. As Carpenter and Sin, op. cit. p. 177 have put it:

> Had the sulfanilamide tragedy occurred at another time, when FDA regulation as the dominant alternative to the *status quo* was not advanced by bureaucratic leaders, the Act would either not have passed or would have taken a much different form.

Thus the tragedy was perhaps a necessary condition, but hardly sufficient, for the passage of the act.

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21. See A. Leslie Florence (1960).
22. See W.G. McBride (1961).
23. See also Steven Spencer (1962). Also Rock Brynner and Trent D. Stephens (2001).
24. See 21 CFR 312.23 "Investigational New Drug Application," §50.20 "General Requirements for Informed Consent," ∫312.23 (a)(6)(iii)(b) "The name and qualifications (curriculum vitae or other statement of qualifications) of each investigator," ∫56 "Institutional Review Boards" (IRB), and ∫56.108(b)(1), ∫312.53(c)(1)(vii), and ∫312.66 on AEs.
25. The critiques of Sinclair's book by a leading meatpacker, Armour, were published in a series of articles in the *Saturday Evening Post*; collected in J. Ogden Armour (1906).
26. Upton Sinclair, as quoted in "Worked on President's Sympathies – Sinclair," *New York Times* (29 May 1906).
27. See also Gabriel Kolko (1963).
28. According to Dr Morris Fishbein, editor of the *Journal of the American Medical Association* (JAMA), "the solvent, diethylene glycol [. . .] rather than the sulfanilamide was responsible" for the poisoning; see "Drug Preparation Blamed in Deaths," *New York Times* (19 October 1937). This statement was made a few days after the first reports of poisoning; the editorial was published as "Deaths following Elixir of Sulfanilamide – Massengill," *Journal of the American Medical Association*, Vol. 109 (23 October 1937), p. 1367. The AMA later published a report on the investigations; see Paul N. Leech (1937).
29. See James H. Young (1983).
30. See "Manufacturer Accused," *New York Times* (12 June 1938).
31. See Arthur Daemmrich (2002).

32. As quoted in Daemmrich (2002), p. 154. See also Frances Kelsey (1965).
33. "Five Die after Taking Tylenol Believed to Contain Cyanide," *New York Times* (1 October 1982), p. A12.
34. Thomas J. Lueck (1982); see also Ernest Holsendolph (1982). Meanwhile, the demand for surveillance cameras in retail outlets grew; see Dorothy J. Gaiter (1982).
35. Michael Decourcy Hinds (1982). The various deadlines established by the regulations were met; Pamela G. Hollie (1983). See 21 CFR 211.132, "Tamper-Evident Packaging."
36. There were further cyanide poisonings using Tylenol capsules. See Peter Kerr (1986); also Robert D. McFadden (1986). According to Abby Goodnough *et al.* (2009), "The poisonings in 1982, which killed seven, terrified the nation and changed the way drugs are packaged, have never been solved."
37. See Dahleen Glanton (2009); Ben Meyerson (2009); and Michael Moss (2009). As President Obama (2009) has recently acknowledged in his speech, "Tougher Food Safety Measures," "the FDA has been underfunded and understaffed in recent years."

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7

Content development: a continuing cGMP training program

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Abstract: As a second example of the content of training materials, this chapter discusses continuing current good manufacturing practice (cGMP) training in four sections. The first section reviews statements taken from regulations and guidances about continuing GMP training, made by the US Food and Drug Administration (FDA) and other regulatory bodies. The interpretive nature of these statements, and the role that risk assessment plays in organizational response to gaps (deviations) between the statements and ongoing behavior, are stressed. The second section addresses the topic of individuals who are qualified to deliver the continuing GMP training, presenting two approaches to qualifying trainers – a formal approach such as a GMP train-the-trainer (TTT) program and an experiential approach. While the experiential approach is cheaper than the formal approach, the formal approach has the merit of reducing variation in employee performance, as well as facilitating root cause analysis (RCA) in case of deviations. The third section reviews major sources of topics that are available for continuing cGMP training, including regulations in 21 CFR 211, written procedures required by these regulations, and topics mentioned in

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FDA guidances, FDA warning letters, and the organization's own records of deviations, investigations, corrective actions and preventive actions, and quality complaints. The final section reviews a major logistical issue in the delivery of continuing cGMP training: the frequency with which this training should be scheduled. FDA recommends training more frequently than just on an annual basis.

Key words: business risk assessment, cGMP requirements, continuing GMP training, FDA warning letters, qualification of SMEs, qualification of trainers, qualified individuals, quality risk assessment, review of forms.

7.1 Introduction

Every organization in regulated industry must train its employees. This training is scheduled in several ways. There is a basic scheduling distinction between training that is delivered in response to a perceived deficiency in performance or qualification, and training delivered according to the calendar. Training according to deficiency in performance or qualification includes new employee orientation (NEO), training for business process redesign and standard operating procedure (SOP) revision, and most technical training. In each case, trainees lack skill, information, or motivation that can be remedied by the training intervention.

Training according to the calendar includes much of regulatory training – the periodic refresher training that is mandated in business ethics, non-harassment policies, non-discrimination policies, a number of Occupational Safety and Health Administration (OSHA) regulations,[1] and current good manufacturing practice (cGMP) regulations. As will become clear in the case of the US Food and Drug Administration

(FDA) regulations, refresher training may be scheduled more frequently than on an annual basis, which is why the regulations and guidance refer to "continuing" cGMP training rather than referring to "annual cGMP refresher training."

The decisions that are made about either kind of training are informed by an implicit or explicit business risk assessment. The level of top-down support and the scheduling of continuing cGMP training reflect a business risk assessment made by various decision makers in the organization. Moreover, decisions about the content of the training, in contrast to mandate and schedule, may also be informed by a quality risk assessment, an assessment in terms of risk to the safety, identity, strength, purity, and quality (SISPQ) of the product.[2]

Consider an example of business risk assessment, as it applies at the program level to continuing cGMP training. Suppose there is a deviation between the number of employees who have documented attendance at the annual cGMP refresher training session and the total number of employees who are required by procedure to attend by the end of the calendar year. In this case, the alert level is any number of employees greater than zero, excluding those on medical leave, etc. The supervisor of an employee who has failed to attend by the beginning of the December recess will be alerted by an e-mail message automatically generated by the organization's learning management system (LMS).[3]

Suppose the total number of non-compliant employees is one. Will this deviation occasion a Notice of Event (NoE) investigation, and corrective action and preventive action (CAPA)? No. What about 10 employees? Probably not. What about a hundred? Perhaps. Even if it does, will the CAPA be fulfilled? There have been cases where the corrective action – simply put, getting the remaining employees trained within a month – had to be extended until the middle of February. And there was no preventive action.

Does this mean that an organization can ignore deviations in processes that have been assessed as low risk? Hardly. The business case for an organizational activity is complemented by the compliance case for that same activity. Continuing cGMP training not only periodically reminds employees of the effect of deviations, rework, etc. on the bottom line, but is a regulatory requirement as well, and reminds employees about the organization's commitment to the regulatory requirements. This commitment carries over to all aspects of regulation.

There are several independent assessments of risk for any process or system in regulated industry, no matter how low or high the level of risk. One is the assessment made by various decision makers of the organization including employees as well as managers, another is the assessment made by regulatory investigators. Both sides are weighing the criticality and complexity of the given process in making their independent risk assessments.[4] The decision makers in the organization must constantly be aware of this intricate interaction between their own business risk assessments and the quality risk assessments of the regulatory investigators, and factor the latter into their own calculation of risk.

The quality risk assessment tends to be reflected in the topics to be presented in continuing cGMP training. The topics reflect in part a quality risk assessment made by various decision makers in the organization, perhaps other decision makers than those making the business risk assessments. Those making the quality risk assessment will be addressing the risk to the SISPQ of the product, and how that topic can be presented as a training topic. The level of risk associated with a process or system that is subject to a given regulation is based on the criticality and complexity of that process.[5] The risk assessment represents the level of risk as well as the acceptable melioration of that risk.

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Take two possible topics for continuing cGMP training, one topic of a higher level of quality risk and another topic of a lower level of quality risk. Suppose the choice was to be made between an episode in a higher risk activity such as aseptic processing and an episode in a lower risk activity such as secondary packaging:

(a) The decision maker(s) should consider the two processes and track and trend relevant deviations, out-of-spec findings, and investigations.

(b) Also, the decision maker should consider the transferability and relevance of each process for the specific training audience. In light of these three factors: risk, transferability, and relevance, the decision maker should estimate the potential training payoff.

(c) Finally, the decision maker should prioritize the episodes in terms of the highest payoff to the organization, and the highest priority example would be highlighted in the training.

The International Conference on Harmonisation (ICH) expressed it well: ". . . the level of effort [. . .] of the quality risk management process should be commensurate with the level of risk."[6] And this level of effort includes training about the topics of the quality risk management process. Both kinds of risk assessment, business and quality, must be taken into account for continuing cGMP training.

7.2 Regulations call for continuing cGMP training

FDA regulations call for continuing cGMP training. The regulations for finished pharmaceuticals are quite explicit:

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> Training in current good manufacturing practice shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with cGMP requirements applicable to them."[7]

Three points in this passage should be highlighted: the training shall be "conducted by qualified individuals," shall be conducted "on a continuing basis," and shall address "cGMP requirements applicable to them."

Some FDA regulations tend to be more implicit. For instance, in the section "Blood and Blood Components," it is stated that:

> All personnel shall have capabilities commensurate with their assigned functions, a thorough understanding of the procedures or control operations they perform, the necessary training or experience, and adequate information concerning the application of pertinent provisions of this part to their respective functions.[8]

The European Union makes a similar point about the need for continuing training in GMPs:

> Besides the basic training on the theory and practice of good manufacturing practice, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given . . .

Health Canada also mandates continuing cGMP training, so that "all personnel are aware of the principles of GMP that affect them, and all personnel receive initial and continuing training relevant to their job responsibilities."[9]

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A rationale for continuing cGMP training is provided in several guidances. For example, the *Quality Systems Approach to Pharmaceutical cGMP Regulations* indicates that "continued training is critical to ensure that the employees remain proficient in their operational functions and in their understanding of cGMP regulations."[10] Likewise, the ICH states, "Training should be regularly conducted by qualified individuals and should cover, at a minimum, the particular operations that the employee performs and GMP as it relates to the employee's functions."[11]

The usefulness of continuing training has been observed outside the area of GMPs. Continuing training in good clinical practices (GCPs), for example, has been recommended for clinical trials staff, as well as for Institutional Review Board (IRB) members.[12]

Hence the FDA regulations provide a mandate for continuing cGMP training. Of course there are interpretive issues regarding these, as any, regulations. As Michael Breggar has correctly put it, "most drug regulations are subject to interpretation."[13] Organizations in the life sciences do not simply react to a regulation; instead there is an intricate interaction between organizational actors at all levels and the various regulations and regulatory regimes, all within a given organizational setting.[14] Between an observation of a gap and an organization's response is a complex decision process. This will occur whether the gap represents a higher level of risk, such as the level of viable particulates in a monitored area, or a lower level of risk, such as one, ten, or a hundred employees failing to attend the annual cGMP refresher training. As already noted, an observation is typically escalated, triaged, and may or may not become a record of interest in the organization's quality management system. Whether the observation will or will not become a record of interest depends upon the risk assessment. It is that record that may

or may not become the basis of an investigation and RCA. Whether the record is investigated further depends upon (possibly a further) risk assessment.

Neither employees nor the organization react to the standard, the regulation – they respond to the observed gap, in terms of risk assessments. The record of the observed gap can also become part of a set of similar records that can be tracked and trended within the quality management system. If necessary, the set itself can be investigated further. Again it is not a matter of reacting to standards, SOPs, or regulations. The organization is responding to the set of excursions, the set of gaps, as reported in the set of records. The conclusion of an investigation can be followed by the development and execution of corrective actions and preventive actions. At each decision node, the decision is based on interpretations and also on risk assessments.

The interpretive aspects and risk assessments of this investigative and remediation process may be more or less explicit in various areas of the life science industry, but the underlying need for interpretation and risk assessment remains. Moreover, since interpretive aspects and risk assessments underlie any organization's response to compliance issues, no organization is simply reactive to regulations.

7.3 Who are the qualified individuals?

FDA regulations mandate that "Training in current good manufacturing practice shall be conducted by qualified individuals."[15] Likewise, Health Canada requires that "Training is provided by qualified personnel."[16]

As Joanne Cochran and Joseph Nally point out, "Since 211.25(a) requires GMP training to be given by qualified personnel, the company should have a procedure and process for qualifying trainers."[17] Such a procedure would list the

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necessary steps (tasks) that, taken together, are sufficient to produce the desired outcome of the process, namely the qualified trainer.[18]

7.3.1 Qualification of SMEs versus trainers

The qualification of trainers is a specific instance of the more general process of qualifying subject matter experts (SMEs). As such, the SOP and process for qualifying trainers will be homologous to the SOP and process for the qualification of SMEs. (The qualification of SMEs will be discussed in the next chapter.) This is not to say that SMEs can be conflated with trainers. There are substantial differences between the two, even though a master trainer can be considered an expert in the subject matter of training.

Crucial differences exist between the kind of process requiring the qualification of a SME and the kind of process (i.e., a GMP training process) requiring the qualification of a trainer. A SME must be qualified, if the following relevant procedure or process:

- involves high skill level, complex activity or application of advanced knowledge or logic;
- is performed in the direct manufacturing of a pharmaceutical product;
- involves the quality attributes (SISPQ) of the product;
- has serious consequences for the batch, negative impact on the patient, or injury to the operator in the case of error or deviation.

These criteria clearly reflect aspects of criticality and complexity that go into risk assessment. By contrast, a trainer must be qualified to present any cGMP training, regardless of complexity and criticality.

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7.3.2 Approaches to trainer qualification

There are two basic approaches to qualifying cGMP trainers. One is a *formal* approach, such as a TTT program; the other is an *experiential* approach, based on management's judgment that an employee is qualified to provide training.[19]

A GMP TTT program provides a formalized approach to the selection of candidates for the training, the delivery of the classroom session, the aspiring trainer's preparation and delivery of a presentation to demonstrate proficiency, and the assessment of the aspiring trainer's performance.

In the case of the experiential approach to the qualification of trainers, management selects the "qualified trainer" based on more or (usually) less explicit criteria and documentation. This approach to trainer qualification is less demanding than the formal approach, including less demand on resources.

The formal approach to the qualification of trainers has several advantages over the experiential approach. Importantly, it tends to homogenize the delivery of training events. This tends to reduce the variation in subsequent performance across trainees (employees).

Human error – Reason's "active failure" – is frequently cited as the root cause of deviations in investigations.[20] The deviation is frequently attributed to a training inadequacy on the part of the employee whose performance has failed, causing the deviation. This training inadequacy, in turn, is attributed to an inadequacy of the trainee, the training event, or the trainer, in some combination. However, if three conditions are met:

1. the trainer has been rigorously qualified in terms of the formal approach;
2. the qualification has been periodically monitored; and
3. tracking and trending of other deviations does not show recurrences, then the trainer and the training event can

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reasonably be removed from consideration in an investigation.

By contrast, it would be implausible to remove the trainer and the training event from root cause consideration if the trainer had been decreed "qualified" by management through the experiential approach.

7.3.3 Staffing considerations

It is most desirable that a qualified trainer, who is also a SME in the topic to be trained, is available to deliver the training. What if such an individual is not available, either in-house or externally? In that case, there seem to be three staffing options that will meet regulatory requirements for cGMP training to be delivered by "qualified individuals."

One option is to have a SME become qualified as a trainer. As Saundra Williams stresses, "Subject matter experts require training in adult learning theory and training techniques before they can adequately train others." As a second point, she notes, "Subject matter experts tend to know much more information than they need to convey. This causes them to overload the learner with information that is unrelated to job needs." Third, she continues, "Ineffective training delivery [by SMEs] wastes dollars invested in instructors, training materials, and employee time." Finally, she points out that, "SMEs who have not been given enough support in the delivery of technical training may cause employees to feel demoralized because they cannot apply the skills on the job."[21]

A second option is to have a qualified trainer become proficient as a SME on the topic to be trained. Linda Elengold cautions, however, that, "it can take the generic trainer weeks, if not months, to get up to speed on a specific process or skill." She concludes: "Many employers believe that it is

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harder to turn a professional trainer into a technically savvy trainer than it is to turn a SME into a trainer."[22]

But there is a third option. Vesper points out that, "sometimes it is difficult to find good trainers who also have solid experience or knowledge in a particular technical area."[23] He goes on to say, "that is an excellent opportunity for co-teaching: an experienced instructor helping to lead the formal sections of the course and the expert serving as a resource to relate experiences and answer questions." He concludes that "if a co-teaching approach is used, both people should be qualified as a team, and that should be provided for in your training SOP."[24] Developing a training team consisting of a qualified trainer and a SME is a most effective way to address the staffing challenge in the short term.

7.4 Applicable cGMP requirements

The FDA regulations stipulate that the training will "assure that employees remain familiar with cGMP requirements applicable to them." What are those "applicable requirements"? Conceptualize the regulatory framework as a pyramid, with the cGMPs at the top, corporate policies making up the next tier, divisional standards as a further tier, and local SOPs as the lower tier.[25] Then the applicable requirements are those that filter down from the cGMPs and are refracted in the local procedures (Figure 7.1).

Topics for continuing cGMP training include not only the regulations in 21 CFR 211, as refracted to the local level, but also any "written procedures required by these regulations, as they relate to the employee's functions."[26] Those written procedures include the following see (Table 7.1).

Suggested topics for continuing cGMP training are also given in several guidances. For example, the *Quality Systems*

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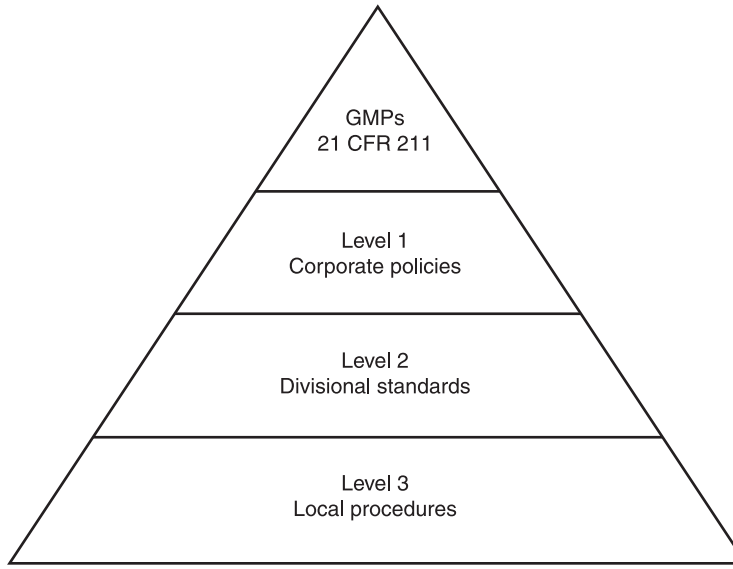

Figure 7.1 Applicable cGMP requirements

Table 7.1 Written procedures required in 21 CFR 211

Regulation	Topic
§211.22(d)	Responsibilities of quality control unit
§211.56	Sanitation
§211.67(b)	Equipment cleaning and maintenance
§211.80(a)	Control of components, containers, and closures
§211.100	Production and process controls
§211.101	Charge-in of components
§211.110(a)	In-process sampling and testing
§211.113	Control of microbiological contamination
§211.115(a)	Reprocessing
§211.122(a)	Materials examination and usage criteria
§211.125(f)	Labeling issuance
§211.130	Packaging and labeling operations
§211.142	Warehousing procedures

(*Continued*)

Table 7.1 (*Continued*)

Regulation	Topic
§211.160(a)	Laboratory controls
§211.165(c)	Testing and release for distribution
§211.166(a)	Stability testing
§211.167	Special testing requirements
§211.176	Penicillin contamination
§211.180(f)	Records and reports
§211.198(a)	Complaint files
§211.204	Returned drug products

Approach to Pharmaceutical cGMP Regulations indicates that "training should address the policies, processes, procedures, and written instructions related to operational activities, the product/service, the quality system, and the desired work culture (e.g., team building, communication, change, behavior)."[27]

Likewise, *Sterile Drug Products Produced by Aseptic Processing* suggests that:

> . . . fundamental training topics should include aseptic technique, cleanroom behavior, microbiology, hygiene, gowning, patient safety hazards posed by a non-sterile drug product, and the specific written procedures covering aseptic manufacturing area operations."[28]

Also, the *Guideline for Quality Assurance in Blood Establishments* suggests that training topics may be derived from a review of

> . . . management observations, proficiency test results, competency evaluations, technical changes, error/

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> accident reports, complaints, QA audits, and problems discovered at critical control points identified in each system within the establishment's total operation.[29]

Another source of topics for continuing cGMP training is the set of FDA warning letters, accessible from *www.fda.gov*. This is an extensive compilation of GXP deviations of all sorts that can be mined for topics. There are two problems that emerge when using these resources.

First, the warning letters refer to companies other than that of the training audience, which tends to blunt the significance of non-compliance, no matter how serious. For striking examples, FDA inspected the Peanut Corporation of America (PCA) in early January 2009 and found "one environmental swab collected on 1 October 2009 from the finished product cooler floor was found positive for *Salmonella*. The swab location was within three feet of pallets of finished product." Moreover:

> . . . mold was observed growing on the ceiling and walls in the firm's cooler used for finished product storage. In addition, water stains were observed running down from the cooling unit fans in the cooler. On 1 October 2009, pallets of finished product were stored directly beneath this unit.[30]

The training audience can easily say, "Yes, these are terrible conditions, but they took place in Georgia."

The second problem is that many times the warning letters do not provide the level of detail needed to develop compelling cGMP training. This is the case even when the warning letter is augmented by newspaper accounts. Again this tends to blunt the significance of non-compliance. It is very clear that something was seriously amiss in the PCA environmental

monitoring program, but it is very hard to pin that down to make training points.

Still another source of topics is the organization's own documentation of deviations, investigations, CAPAs, and product quality complaints, as captured in the quality management system. This documentation can be reviewed on a periodic basis, say quarterly or even monthly. The selected record can be worked up and presented in a training module. These records do not suffer from either of the shortcomings noted for the FDA warning letters. The organization's documentation refers to the training audience's own systems, and some members of the audience may have been involved in the observation, investigation, and remediation process. Second, the very demands for compliance and documentation in the organization's investigation and remediation SOPs should ensure an adequate level of detail to make training points.

Take an illustrative example, one that might be a suitable topic for a quarterly cGMP training session. Recently, warehouse staff had trouble correctly filling out a particular form. Supervision caught the problem several times, while countersigning the document. Then supervision missed one, and it was recorded in the quality management system. Management was alerted, and requested an investigation of the problem – was it a matter of employee training, procedure, form design, or what?

During the investigation, training records were reviewed, and it was evident that each of the warehouse employees had been trained on the current version of the SOP by a qualified trainer. The SOP was reviewed. It looked straightforward on its face, and because it also covered two other forms for which no problems had been observed, it was given a clean bill of health. The form itself was reviewed, in terms of a checklist.[31] (Table 7.2).

Table 7.2 Checklist for the review of forms

■ **Who is the business owner of the form?** If there was no specified business owner of the form, no one would be responsible for the integrity of the form, and perhaps more important, anyone could make changes to the form. These uncontrolled changes result in incoherence of the form.
■ **Were user requirements gathered?** Gathering user requirements during planning for the form should trump managerial decree for content and structure. User requirements include answers to the following: ■ Who fills out the form? ■ What is the form's purpose? ■ What is the time frame for using the information in the form? ■ Are there duplicate users of the form?
■ **What is the structure and flow of the form?** The structure and flow of the form should comprise a linear progression, upper left to lower right.
■ **Is the form focused?** The form should be succinct rather than wordy.
■ **Are there instructions for the form?** If there are instructions, they should be included on a separate section or separate page, rather than interspersed within the form itself.
■ **Was there expert review of the form?** Critical review by SMEs can frequently point out problematic aspects of a form, which should be addressed before finalizing the document.
■ **Was there usability testing of the form?** It is critical to pilot the penultimate draft of the form then make revisions in light of the experiences and criticisms of a sample of end users.

During the review of the form, it became clear that there were several serious content and formatting issues. When the form was redesigned, the warehouse staff's trouble filling out the form ended. The problem seems to have been resolved. It is worth noting that re-training of the warehouse employees was not required, since training was not identified as the root cause of the problem, but the employees had to be trained on the rectified form.

This illustrative account could be proposed to the training council or other appropriate group and, if approved, could be worked up into a continuing cGMP training module. It would be of interest to the organization's staff, because it refers to their warehouse, they may know the form in question, they may know some of the employees who were involved in the problem, and they will be pleased to see the satisfactory outcome of the investigation.

Perhaps the best approach to sources of topics for continuing cGMP training is a combination of local problems gleaned from records in the organization's quality management system, with direction provided by the most serious compliance problems, as indicated by FDA warning letters[32] (Table 7.3). For instance, one recurring topic from fiscal years 2005 through 2008 has been 21 CFR 211.22, "Responsibilities of Quality Control Unit." Should the organization's records

Table 7.3 **Most serious GMP problems in FDA warning letters, FY 2008**

Regulation	Topic
§211.192	Production record review
§211.160	Laboratory controls
§211.100	Written procedures; deviations
§211.22	Responsibilities of quality control unit
§211.42	Design and construction features
§211.84	Testing and approval or rejection of components, containers, and closures
§211.110	Sampling and testing of in-process materials and drug products
§211.113	Control of microbiological contamination
§211.165	Testing and release for distribution
§211.188	Batch production and control records

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provide any instances of such problems, the FDA warning letters might give additional weight to the training points.

A final point about applicable cGMP requirements is the relevance and effectiveness of particular cGMP training for various groups within an organization's workforce. In *Q9, Quality Risk Management*, the ICH has suggested that a potential use of quality risk management principles and tools may be "to determine the appropriateness of [. . .] ongoing training sessions based on education, experience, and working habits of staff."[33] Trainees can be grouped according to their task assignments. For example, employees who check batch records need not be given the same continuing cGMP training module as operators, even though both groups may be governed by the same broad set of procedures. Their workplace focus is much different. Likewise, ICH recommends that the appropriateness of continuing training be determined by "a periodic assessment of previous training (e.g., its effectiveness)."[34]

7.5 Logistics of continuing cGMP training

Having discussed the regulatory requirements for continuing cGMP training, the necessity of using qualified trainers to deliver the training, and the topics that could make up the training content, it is time to turn to the logistics of this training. The main logistical question is: How frequently should this continuing training be scheduled?

FDA regulations do not stipulate the frequency of continuing training, but recommendations are available in guidances. For example, the *Current Good Manufacturing Practice for Medical Gases* indicates that, "FDA recommends that cGMP training not be conducted in one massive training session.

Rather, it should be presented in smaller more manageable sessions held throughout the year, or at a minimum be held once a year."[35] Speaking at an FDA workshop, compliance officer Duane Sylvia suggested that, "cGMP training should be revisited at frequent intervals and needs to be conducted by qualified individuals." He continued, "Conducting cGMP training once a year is not recommended, but instead should be presented in smaller more manageable portions, presented throughout the year with documentation of the type, time, and attendance of each session."[36]

Some regulated organizations have developed very elaborate schemes to schedule continuing cGMP training. One example will suffice. An organization required each employee to attend day-long refresher training at a specified location on the first Monday of the employee's birth month. There was one makeup day a year for employees who missed their scheduled date. The training agenda was fixed for the entire year, regardless of intervening events. It incorporated OSHA, cGMP, business ethics, and other refresher training, as well as a "Meet the CEO" session. Given the packed agenda, less than an hour was devoted to cGMP topics. Birthday cake was provided to each attendee. Nonetheless, this scheme was simply a variant of the "one hour, once a year" cGMP training schedule.

Regarding industry practices, James Vesper has stated that "most companies conduct formal GMP training or reinforcement training at least annually; some do it twice a year; a few do it quarterly."[37] There are business considerations as well as regulatory issues here. More generally, John McConnell has indicated "How often the training course is to be conducted depends on several factors, including:

- employee availability;
- total number of current employees to be trained;

- maximum size of training classes and method;
- required time to conduct training;
- projected future training population."[38]

All of these factors should be taken into account in planning for continuing cGMP training.

7.6 Conclusion

This chapter addressed continuing cGMP training in four sections. The first section reviewed the statements that FDA and other regulatory bodies have made in regulations and guidances regarding continuing cGMP training. The role that interpretation and risk assessment plays in an organization's response to gaps (deviations) between the statements and ongoing behavior was stressed. The second section considered the "qualified individuals" that deliver this continuing training, including similarities and differences between qualification of trainers and qualification of SMEs. A formal approach to qualifying trainers such as a cGMP train-the-trainer program was compared to an experiential approach such as management's judgment that an employee is qualified to provide training. The experiential approach is cheaper than the formal approach, but the formal approach has the merit of reducing variation in employee performance, as well as facilitating RCA in case of deviations, as the next chapter will discuss in some detail.

Also, various staffing options were examined. The third section reviewed topics that are suitable for continuing cGMP training. Sources included cGMP regulations in 21 CFR 211, written procedures required by these regulations, topics mentioned in several FDA guidances, FDA warning letters, and the organization's own records of deviations,

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investigations, CAPAs, and product quality complaints. The final section addressed the logistics of such training, including the frequency with which cGMP training should be delivered, concluding that FDA recommends training more frequently than just on an annual basis.

7.7 Notes

1. See OSHA, 29 CFR 1910.134(k) Respiratory Protection, "The employer [is required] to provide effective training to employees who are required to use respirators. The training must be comprehensive, understandable, and recur annually, and more often if necessary." See also ∫1910.134(k)(5), "Retraining shall be administered annually."
2. For the distinction between quality risk assessment and business risk assessment, see Chris Enyinda, Charles Briggs and Khalid Bachkar (2009); for the distinction in the GLP context, see Alain Piton, (2008); for the distinction in the GCP context, see Sherri A. Hubby (2009).
3. On the one hand, such an e-mail message would be exempt from Part 11 considerations. Among the few training related predicate rules that are covered by 21 CFR 11, *Electronic Records; Electronic Signatures*, is 21 CFR 111.14(b)(2), which stipulates "Documentation of training, including the date of the training, the type of training, and the person(s) trained," relating to GMPs for Dietary Supplements. [Published in the *Federal Register*, Vol. 72, No. 121, 25 June 2007, p. 34810]. However, the message itself can include the proviso that "This message is not a GMP document; for GMP purposes, refer to the source document in the LMS," etc.

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4. See FDA, *Pharmaceutical cGMPs for the 21st Century – A Risk-Based Approach, Final Report-Fall 2004*, September 2004. See also John Gardner's comments, as reported in Joseph Pickett, "GMP audit imminent after 6-year inspection gap, states 2007 risk-based model: Gardner," *Validation Times*, September 2007.
5. See International Conference on Harmonisation (ICH) (2005).
6. ICH, *Q9, Quality Risk Management*, op. cit., p. 2.
7. 21 CFR 211.25(a), Personnel qualifications.
8. 21 CFR 606.20, Personnel. The relevant phrase is "adequate information concerning the application of pertinent provisions of this part to their respective functions."
9. See European Union (2009) ∫2.9. Health Canada (2009), Regulation C.02.006. ∫6.
10. See FDA (2006). Thus a business rationale as well as a compliance rationale can be made for continuing training. For the business rationale, see Anne Garstka and Donald E. Hagman (2000), "training must be continuous. By providing continuous training, pharmaceutical companies instill good habits that lead to safe, effective products and higher profits."
11. International Conference on Harmonisation (2001), ∫3.12. [Published in the Federal Register, Vol. 66, No 186, 25 September 2001, pp. 49028–49029.]
12. Regarding clinical trials staff, see Barry Strack (2005), "the incorporation of continued training is an important element that many popular programs neglect to focus on." See also Akanksha Saxena (2005), "management should see to it that there is continuous training of SOPs among the staff." Also US Department of Veterans Affairs (2003), VHA Directive 2003-036, requires "appropriate training in the ethical principles and good

clinical practices for human subjects research on an annual basis." Regarding institutional review boards, see, for instance, Jeffrey Cooper and Pamela Turner (2006), who state "An institutional review board (IRB) 'shall be sufficiently qualified through the experience and expertise of its members . . . to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.' Meeting this regulatory requirement requires initial and continuous training" (p. 313). They are citing 21 CFR 56.107, IRB Membership.

13. See Michael Breggar (2009).
14. Interpretive issues about observations arise on the regulatory side as well. Consider the FDA 483 observation to MedImmune dated 29 March 2007 "on 28 March 2007 [. . .] an operator was observed cleaning his/her personal prescription glasses in the ISO Class [. . .] area." Compare that to FDA warning letter to MedImmune dated 24 May 2007: "On 28 March 2007, an operator was observed removing his/her safety glasses, then removing and cleaning his/her prescription type glasses, thus allowing for skin to be exposed." Available from: *www.fda.gov/downloads/AboutFDA/CentersOffices/ORA/ORAElectronicReadingRoom/UCM056161.pdf* and *www.fda.gov/ICECI/EnforcementActions/WarningLetters/2007/ucm076398.htm*
15. 21 CFR 211.25(a), Personnel qualifications.
16. Health Canada (2009), Regulation C.02.006, ∫6.1.
17. See Joanne W. Cochran and Joseph D. Nally (2006).
18. "Standard operating procedures (SOPs) are sequences of steps for workers to follow to complete tasks." See Mark Edelman (2003).
19. See Cochran and Nally, op cit., "Minimum requirements for trainers may include some formal education (e.g.,

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Train-the-Trainer course) or experience in presenting training . . ."

20. See Table 7.3. As Breggar, op. cit., p. 26 has aptly put it, "Generally speaking, most FDA citations appear technical. But their root cause is nearly always managerial issues that impede the performance of people."
21. Saundra Wall Williams (2001) cites Anthony P. Carnevale *et al.* (1990); Ruth Colvin Clark (1994); and Steve Trautman and Kate Klein (1993). See also Cochran and Nally, op. cit., "Often the person who has the best technical knowledge is not necessarily the best trainer."
22. See Linda Elengold (2001).
23. See J. Vesper (2000).
24. Vesper, op. cit. This is a short-term option; in the longer term, management will likely prefer a SME becoming a qualified trainer, or a qualified trainer becoming a subject matter expert.
25. See also Willem PA van der Tuuk Adriani and Smit Sibinga (2008).
26. 21 CFR Sec. 211.25(a), Personnel qualifications.
27. See FDA (2006) *Guidance for Industry: Quality Systems Approach to Pharmaceutical cGMP Regulations*.
28. See FDA (2004), *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice*.
29. See FDA (1995).
30. Available at *www.fda.gov/downloads/AboutFDA/CentersOffices/ORA/ORAElectronicReadingRoom/UCM109834.pdf* These are but two of an extensive series of observations.
31. See Jakob Nielsen and Rolf Molich (1990); Jakob Nielsen, Kara Pernice Coyne and Marie Tahir (2001); and Jakob Nielsen (1994). While Nielsen and his

colleagues address software and web usability issues, the principles of end-user and heuristic usability testing apply to paper-based forms as well.

32. See Gerhard Becker (2007), for fiscal years 2005–2006, and Gerhard Becker (2009), for fiscal years 2006–2008.
33. See ICH (2005), op. cit., p. 15.
34. See ICH (2005), ibid.
35. See FDA (2003).
36. See Duane Sylvia (2000). See the interview with Kristen Evans, A CDER official offers tips on inspections, *CDER Inspection Tips*, Salt Lake City: Master Control (2000), p. 4: "Training should not be a one-shot deal. It has to be ongoing and dynamic."
37. See James L. Vesper (2000), op. cit., p. 29.
38. John H. McConnell (2003).

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8

Content development: qualification of employees

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Abstract: As a third example of the content of training materials, this chapter focuses on the topic of employee qualification, a critical kind of training that can follow remediation in regulated industry. It further provides a comprehensive framework for an organizational approach to employee qualification. A typology of training is presented. Specific employee qualification considerations, including employee qualification as process, qualification status, and measures to demonstrate qualification are discussed. Employee qualification should be based on an assessment of complexity and criticality of the procedure. These concepts demonstrate an organized approach to employee qualification, compliant with regulatory requirements and expectations, and consistent with modern principles of risk analysis.

Key words: awareness training, critical procedures, employee disqualification, employee qualification, employee requalification, installation qualification (IQ), Ishikawa diagram, memory (types of), operational qualification (OQ), performance qualification (PQ), process of qualification, qualification of SMEs, "Read and sign" training, skill demonstration assessment (SDA).

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8.1 Introduction

This chapter discusses qualification of specific categories of employees in a GXP environment. Employee categories addressed include production operators and technical subject matter experts (SMEs). These personnel are designated for specific critical tasks in an organization. Concepts discussed herein are also applicable to laboratory analysts. This chapter is the third illustration of the development of training content, following the previous discussions of new employee orientation programs, associated GXP training, and continuing current good manufacturing practices (cGMP) training programs.

The first part of this chapter discusses types of employee training, including awareness training, training *per se* (which includes a paper-and-pencil assessment), employee qualification (i.e., training that includes a skill demonstration), and qualification of SMEs. The second part addresses types of qualification, including employee qualification as process and as status, as well as the use of SDAs in employee qualification.

The third part focuses on the rationale for qualification, highlighting the role the qualification process plays in deviation investigations and root cause analyses (RCAs). This part also considers the criteria for deciding what kind of training is appropriate for a specific procedure; this depends on the complexity and criticality of the procedure and the associated process. The final part delineates two other aspects of the qualification process, employee disqualification and employee requalification.

8.2 Regulatory basis for training

FDA requires employees in all regulated areas to be trained. For example, 21 CFR 58.29 states: "Each individual engaged

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Table 8.1 FDA regulations for employee training

Regulation	Regulated personnel
21 CFR 58.29	Non-clinical lab personnel
21 CFR 110.10	Human food handlers personnel
21 CFR 113.10	Thermally processed food handlers
21 CFR 114.83	Acidified food processing handlers
21 CFR 120.13	HACCP systems managers
21 CFR 123.10	HACCP systems managers
21 CFR 211.25	Pharmaceutical personnel
21 CFR 225.10	Medicated feed personnel
21 CFR 600.10	Biological products personnel
21 CFR 606.20	Blood component personnel
21 CFR 820.25	Medical device personnel
21 CFR 1271.170	Human tissue recovery personnel

in [. . .] a nonclinical laboratory study shall have education, training, and experience, or combination thereof, to enable that individual to perform the assigned functions."[1] This requirement is repeated, with slight variation in phrasing, for other regulated areas (Table 8.1). FDA regulations say little more about training requirements. According to John Levchuk of the FDA, "The FDA has not published a guideline establishing acceptable procedures for personnel training, nor is a guideline being planned." This point was reiterated by Vasilios Frankos, who stated, "At this time we have no plans to provide companies with training materials for their employees."[2]

Several FDA guidances for industry provide more direction for training. In the *Quality Systems Approach to Pharmaceutical cGMP Regulations*, for example, FDA indicates:

> Under a quality system, managers are expected to establish training programs that include the following:

- evaluation of training needs;
- provision of training to satisfy these needs;
- evaluation of effectiveness of training;
- documentation of training and/or re-training.

When operating in a robust quality system environment, it is important that managers verify that skills gained from training are implemented in day-to-day performance.[3]

FDA has thereby provided an opening for each organization in regulated industry to develop its own training system that will ensure that its employees are appropriately trained for GXP compliance.

One often overlooked functional area where the use of standard operating procedures (SOPs) makes good business sense is in employee training. The development of a half-dozen or so training system SOPs – providing guidance for a number of areas such as task analysis, design and development of training and assessment materials, program rollout and evaluation, SME qualification, structured on-the-job trainer (SOJT) qualification, training advisory council of middle managers, and training metrics – would go a long way toward economizing an organization's training resources. Some suppose that these SOPs would add to the "training burden" of the organization; our experience strongly suggests that the "burden," such as it is, derives from the very absence of procedures. While training is a regulatory requirement, there is no requirement for the use of SOPs to guide and structure those training activities.

8.3 Categories of training

Before discussing qualification of employees for GXP compliance, let us first describe the respective categories and/

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Kind of training	Awareness training	Training *per se*	Employee qualification	Qualification of SMEs
Characteristics	No assessment	Training plus KTA	Training plus SDA	Qualification across relevant SOPs
Level: Lo → Hi				

Figure 8.1 Complexity of training

or levels of training in the organization. It is possible to identify several levels of training in an organization. They make up a series, ordered by the complexity of training activities. From lowest level of complexity to highest, they include awareness training, training *per se*, qualification, and qualification of SMEs (Figure 8.1).

8.3.1 Awareness training

Awareness training, or familiarization training, is an activity that involves conveying subject matter to an audience, with the goal of making the audience aware of the content of the communication. This activity can barely be called training. The subject matter being communicated can be informational or actionable. An example of informational content is an organization's announcement that layoffs will begin on a specific date. An example of actionable content is an announcement that the South Corridor will be closed for renovation beginning next week, and pedestrians should use the North Corridor until further notice.

Awareness training can take the form of a mass meeting in an auditorium, a "read-and-sign" document that is circulated to all affected personnel, an e-mail message, etc. Awareness training is typically documented by having the audience members sign attendance sheets, the buck sheet on a "read-and-sign" document, etc.[4]

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In many organizations, "read-and-sign training" constitutes the bulk of training conducted. Organizations are now evaluating the appropriateness of "read-and-sign training" for certain types of procedures. Many times, implicit in this type of training is the organization's need to exhibit due diligence to reduce its liability. The trainee signature is evidence of the organization's due diligence.[5] Procedures for which "read-and-sign training" is not appropriate are being transitioned into the next higher level of training.

8.3.2 *Training* per se

The next higher level is training *per se*, sometimes called facilitation. This is an act of communication that intends to improve the workplace proficiency of members of the audience. Training *per se* includes the trainer (facilitator) or trainers, trainee(s) with various skill set(s) and disposition(s), training materials (including the training script) and assessment materials, training organization (i.e., supervisory factors, business case), facilities (i.e., allocated space, allotted time, utilities), and auxiliary materials (i.e., instruments and equipment, raw and in-process materials used in the training), etc. Training *per se* includes several delivery modalities, such as e-learning, mentoring, and classroom delivery.[6] The organization and its environment, within which the training activities, training organization, and training facilities are located, are also important for situating employees and their tasks. These categories can have a profound impact on the conduct and effectiveness of training *per se*.

Finally, training *per se* is complemented by an assessment that allows the trainer to assess whether the training intervention had (or did not have) the desired impact on the

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job, in the workplace.[7] That typically takes the form of a knowledge transfer assessment (KTA), a paper-and-pencil quiz that predicts performance on-the-job. If trainee proficiency or non-proficiency has been correlated with a quiz score, so that high scores correlate with task proficiency and low scores correlate with non-proficiency, then the KTA is validated, and performance on-the-job can be predicted from trainee performance on the KTA.[8]

8.3.3 Employee qualification

At the third level, employee qualification is a kind of training augmented by a SDA. Employee qualification on a procedure or process is performed by a qualified trainer who is also a SME, or by a team consisting of a qualified trainer and a SME. The SME must have expertise in the procedure or process on which the trainee is qualifying. The qualified trainer is responsible for the documentation of the qualification event. The training is often conducted under SOJT programs. In the case of the team training, the trainer and the SME are jointly responsible for the documentation.

Employee qualification differs in several ways from training *per se*. Perhaps most importantly, training *per se* and qualification involve different systems within the brain of the trainee. Training *per se* tends to involve the declarative memory system, while employee qualification tends to involve the procedural memory system (Figure 8.2).

Both declarative and procedural memory systems are elements of long-term memory, as contrasted to short-term or working memory. Declarative (including semantic and episodic) memory is an explicit form of memory, where facts are stored and can be recalled and "declared." Procedural memory, by contrast, is an implicit form of

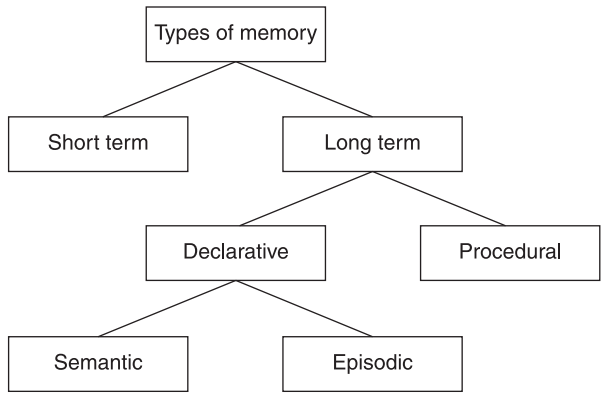

Figure 8.2 Types of memory

memory, whereby performances can be elicited without conscious thought.

The episodic memory system is related to the location or time of a personally-experienced event; an example would be the content of a particular training event that this trainee attended. The semantic memory system is related to facts that are not based on any personal recollection of episodic memory. An example would be identifying the pharmaceutical company with the highest global sales figures. The procedural memory system is related to a skill, such as motor or cognitive performance; an example would be operating a forklift truck.[9]

How do these memory systems relate to kinds of training? Training *per se* includes a paper-and-pencil assessment (KTA), which consists of recalling information provided in a particular training event, or else general knowledge such as the name of the book that Upton Sinclair published in 1906. Thus training *per se* engages the declarative memory system, either episodic or semantic.

Employee qualification involves a SDA that consists of the trainee independently performing the requisite workplace

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tasks, while being monitored and assessed by the trainer. Thus qualifications engage the procedural memory system. During the actual performance, the trainee may or may not be able to provide a declarative account of the task performance. If the trainee's performance is indeed independent, it would not be recommended that the trainer engage in dialogue or ask questions. Instead, the "tell, show, do, and follow-up" cycle of SOJT can be augmented by a debriefing, wherein the trainee can give a declarative account should the trainer so desire.

8.3.4 Qualification of SMEs

The final kind of training is the qualification of SMEs. Employees are designated as SMEs in two ways. One is an experiential approach, based on management's designation that an employee is a SME; the other is a formal approach, such as successfully completing a qualification program. Thus the process for qualifying SMEs is homologous to the process for qualifying trainers.

While the experiential approach may involve training of management to utilize specific criteria, to exercise good judgment, and to complete relevant documentation when designating this or that employee a SME, it does not involve employee training.

The formal approach to the qualification of SMEs does involve training. This kind of qualification is typically instituted by organizations that need to document that their SMEs are qualified, for instance if the organization is operating under a consent decree. Under such conditions, not only will the process of designating SMEs be formalized, but the role of SMEs in the writing of SOPs will be proceduralized as well.

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Under these conditions, SMEs become qualified when they have successfully qualified on a number of SOPs that address the competences of their subject matter. The business owner usually identifies the particular SOPs that characterize the subject matter. The ensuing employee qualification process has two elements: overview training and skills training. Overview training (i.e., training *per se* that provides an overview of the subject matter), tends to be more conceptually focused, while skills training tends to be more performance oriented. Concepts tell what a thing is; tasks describe how to do something. Concepts provide the "science" for task performance. For example, the process of sanitizing equipment might be conceptualized as "reducing the levels of microorganisms and particulates to acceptable limits," thereby minimizing the risk of product contamination from the equipment.

Overview training may be delivered by a qualified trainer in a classroom. There will be a SOP that will be the basis of this overview training, as well as a KTA. The event is documented in a training record where the facilitator and trainee concur that the trainee has successfully concluded the training (or not). Should the trainee be unsuccessful in the overview training, by procedure the trainee will have options such as repeating the training event at a later date, etc.

Once the overview training is successfully concluded, the trainee goes on to the SOJT events. The qualification event will usually be conducted one-on-one by a SME who is also a qualified trainer, as a SOJT event. There will be a SOP for each of the SOJTs in the module, as well as a SDA for each. The completed SDA form is then entered into the training tracking system.

Consider the typical SME qualification process for the use of vaporized hydrogen peroxide (HPV) for sterilizing controlled areas.[10] That SME individual training plan (i.e.,

curriculum) might include the following three modules and associated training events.

Figure 8.3 displays the initial module, which would include an introduction to cleaning, sanitization, and sterilization, followed by a SOJT session on facility cleaning. The training content would reflect 21 CFR 211.56(b) and (c), and the written procedures mandated there.

Figure 8.4 displays the next module, where the overview session might include further discussion on cleaning, sanitization, and sterilization. This is followed by one SOJT session on clean-in-place and another on sterilize-in-place.

Figure 8.5 displays the final module in the training curriculum, which might include an overview of sterilizing with HPV, followed by one SOJT session on storage, handling, and preparation of hydrogen peroxide and another SOJT session on introducing HPV to a room, managing the sterilization cycle, and assessing the

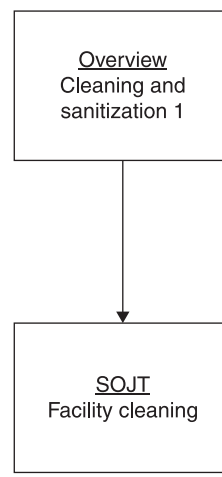

Figure 8.3 Initial module

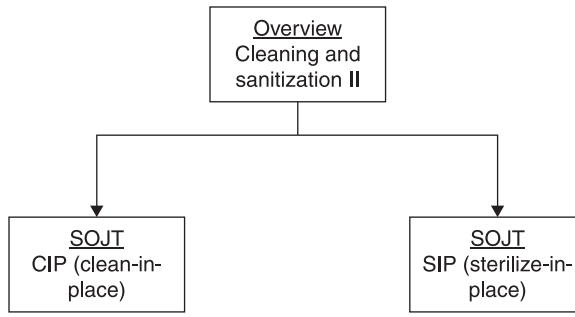

Figure 8.4 Second module

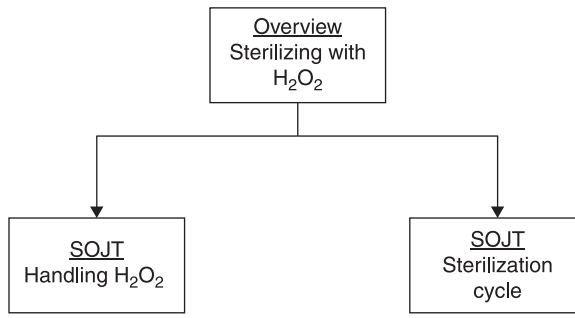

Figure 8.5 Last module

outcomes of the process. If the trainee's performance is assessed as less than successful, by procedure this would be recorded in the training tracking system, and the trainee would be advised of the various options, including repeating the training process, etc.

After the trainee has been successfully trained to the relevant SOPs, and the three training records and the five SDAs have been entered into the training tracking system, the trainee is fully qualified. This means the trainee is ready to function independently as a SME in the use of HPV for sterilizing controlled facilities.

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8.4 Qualification considerations

Qualification, in general, means fitness for some purpose, demonstrated by meeting necessary conditions or qualifying criteria. In regulated industry, "qualification" is used on the one hand in a process sense and, on the other hand, in a status sense. "Qualification" can mean the process of becoming qualified. This is "qualification" as a process, for instance "the qualification of the equipment on Line 28 is complete." Closely associated with that usage is "qualification" as a status, as in "the hiring manager said that the candidate had all the qualifications for the position."

8.4.1 Qualification process

Qualification as a process can be applied to anything (e.g., equipment, instruments, facilities, and computer systems). As Steven Ostrove states, "equipment, or systems, actually used as part of the production process for the production or manufacturing of a pharmaceutical or medical device product must be qualified prior to its use." It can also be applied to personnel. Ostrove goes on to acknowledge that "the term 'Qualification' appears twice in Title 21 of the CFR: 21 CFR 211.25 – Personnel qualifications (and) 21 CFR 211.34 – Consultants."[11] According to the well-accepted approach to equipment qualification, there are three main phases to the qualification process: Installation qualification (IQ), operational qualification (OQ),[12] and performance qualification (PQ).[13]

These three phases – IQ/OQ/PQ – can also usefully be applied to the process of qualification of personnel, as follows:

- Personnel IQ may be likened to providing objective evidence that the prospective trainee have the requisite

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education and background for the relevant SOP. If the SOP lists several prerequisites, documented evidence must indicate that the prospective trainee has completed training on each of these.[14]

- Personnel OQ may be likened to providing objective evidence that the trainee can function in the training situation (event) in an appropriate fashion. In a SOJT event, for example, this means the trainee performance is within the "control limits" set by the SOP. In the last analysis, this means that the trainee can perform the task correctly and independently.[15]
- Personnel PQ may be likened to the demonstration of acceptable performance during representative operational conditions. The trainee's activities (e.g., on the shop floor or at the lab bench at the close of training) consistently produce a product that meets the standards set by the SOP or manufacturing order. In the GMP framework, the performances are directly related to the quality attributes (i.e., the SISPQ) of the regulated product.[16]

Once the process of employee qualification is successfully completed, employees are qualified, and remain so unless and until they become disqualified.

8.4.2 Qualification status

Qualification as status, sometimes called certification, characteristically applies to persons. For instance, employees are sometimes designated SME because they are the originator of a new SOP. The reasoning for this practice is the following. An SME on a given SOP, who is a qualified trainer,[17] can train another employee on that SOP. But who will provide the training to a new SOP? Who is to be the first mover? For a new SOP, there must be at least one SME, or compliant

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training will never occur. Those SMEs must be designated by management (in this case, the business owner), not because they have been through a qualification process, there is not any, but because they are the originator of the SOP, which is a status.

Occasionally an organization will develop a procedure that indicates employees are qualified when they have successfully executed the procedure three times. To be distinguished from various certified fellow employee (CFE) approaches to training, this approach requires neither a SME nor a qualified trainer. However, it appears to violate the predicate rule, personnel qualifications, which stipulate that "Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have the education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions."[18] This means that employees must be capable of performing assigned tasks prior to touching the regulated product. They already have the educational, training, and experiential status – they are not "learning as they go."

8.4.3 Qualification measures

Qualification measures consist of SDAs. A training procedure for employee qualification stipulates how, when, and where the trainee can independently perform the task on relevant equipment.

The training procedure will also stipulate that the trainer use a controlled form that is the SDA checklist. The SDA checklist has fields for entering the number and version of the relevant operational SOP. The checklist also includes a number of items that describe the identified critical or representative tasks to be assessed on the SDA. These are the items assessing the trainee's performance (Figure 8.6). The

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Name of SOP: _____ SOP #: _____ Version #: _____		
Trainer: Monitor the trainee's performance and check each of the following items: "yes" if the performance was successful, "no" if not.	**Yes**	**No**
Demonstrate correct mopping technique for cleaning and sanitizing tasks.		
Demonstrate correct techniques for using wipes on horizontal and vertical surfaces during cleaning and sanitizing tasks.		
Perform the daily and weekly cleaning and sanitizing tasks for the controlled area.		
Perform the monthly and quarterly sanitizing tasks for the controlled area.		
Document cleaning and sanitizing data on the *Cleaning and Sanitization Log* for the controlled area.		
Trainee signature: _____	**Date:** _____	
Trainer signature: _____	**Date:** _____	

Figure 8.6 Illustrative SDA for sanitization program

trainee performs and the trainer (or some other SME) monitors the performance and checks each item in turn: "yes" if the performance was successful, "no" if not. When the performance is complete (whether successful or not), the trainee and the trainer sign and date the SDA. Area management may sign as well. The completed checklist is submitted to the data entry personnel of the validated training tracking system or, in case of manual data processing, to the staff of the document repository.

8.5 The rationale for qualification

Why should an organization qualify something or someone – be it equipment, computer system, facilities, or personnel? As we saw in Chapter 2, the stakeholders of an organization

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can observe various problems – an out-of-spec lab result or a manufacturing deviation, say – and report those problems to management. The responsible manager can initiate an investigation into the root cause of the probelem. Once the investigation report is complete, the manager can than implement an appropriate remediation.

Candidates for the root cause of the problem include such process elements as equipment, facilities, procedures, raw materials, utilities, employee performance, etc. Consider the Ishikawa diagram displayed in Figure 8.7. The investigation proceeds along the same lines as we have discussed in Section 2.2, "The process of investigation." Candidate elements are considered and eliminated from consideration, until only one remains. That remaining element is labeled the "root cause." An element is removed from consideration once it is determined that it could not have been the root cause of the deviation. That is where the process of qualification becomes important. An excellent way to eliminate an element from further consideration as a root cause of a problem is by qualifying that element in advance.

Take equipment, for example. Installation qualification ensures that a piece of equipment, say an autoclave, has been installed within design specifications. Operational

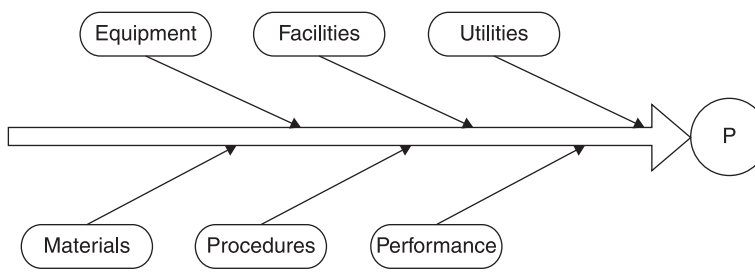

Figure 8.7 Main elements

qualification ensures that the autoclave operates as designed and as required by the user. Performance qualification ensures that the autoclave displays continued suitability for its intended use. The IQ, OQ, and PQ of elements are critical for pharmaceutical, biotech, and medical device manufacturing and lab systems. Pharmaceutical, biotech, and medical device companies all must install, operate, and maintain equipment to be used in the manufacturing and laboratory system within design specifications, ensuring their operations are reliable and the quality of the output or product is consistent. In this case, the output of the autoclave is sterilized instruments.

When an autoclave is qualified, it is ensured that it has been installed according to design specifications, it operates in a reliable fashion, and that its output or product has a uniform (and high) quality. Thus the autoclave will not vary from design specifications upon installation. The autoclave will not vary from its specified range during the operation of the system. And its output, sterilized instruments, will not vary from the desired level of quality. Because there has been no variation of the autoclave that has been qualified, it cannot be the cause of the manufacturing deviation or out-of-specification lab result. Through the qualification process, that element can be eliminated from consideration in an investigation.

As the various elements are eliminated, the set of candidates for "root cause" decreases. Suppose the only elements remaining are raw materials and employee performance (Figure 8.8). The same approach can be applied to the performance element (i.e., employee performance). At some point the employees working on the process that generated the deviation had been trained on the relevant SOPs (or not). The constituents of the performance element include employees (who were the trainees), their trainer(s), the

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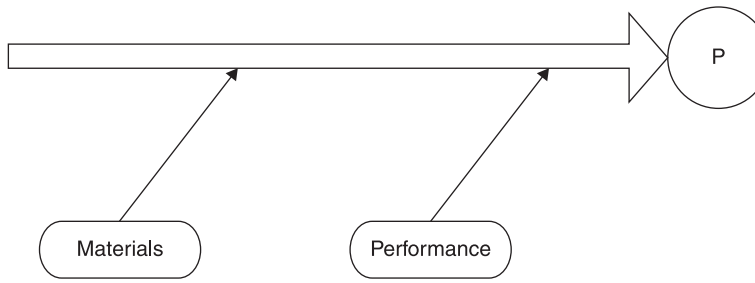

Figure 8.8 Qualified elements eliminated from diagram

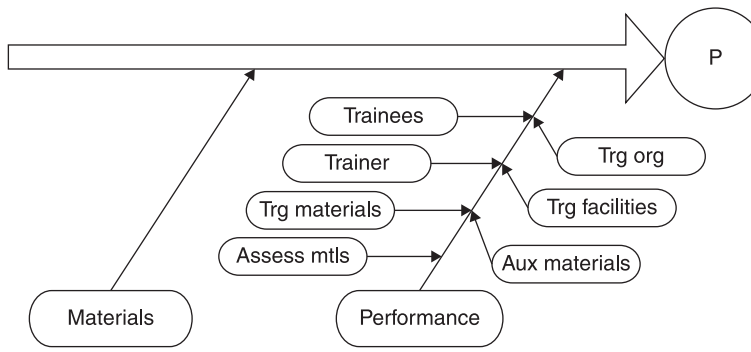

Figure 8.9 Constituent elements of employee performance

training materials and assessment materials, the training organization, facilities, and auxiliary materials utilized in training (Figure 8.9).

Each constituent element is considered and eliminated from consideration when it is determined that it could not have been the root cause of the deviation. The process of employee qualification provides an important way to eliminate a constituent element in advance.[19]

Was the trainer qualified? Were the employees (trainees) qualified? Remaining constituent elements can be analyzed in further detail. Thus if the training organization remains,

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it can be further analyzed into supervisory factors and business case. If the employees (who were the trainees) remain, they can be further analyzed in terms of skill set(s) and disposition(s). Was their morale low? If the category training facilities remains, it can be further analyzed into allocated space, allotted time, and utilities. Were the location and time adequate and appropriate? If the constituent element Auxiliary Materials remains, it can be analyzed into instruments and equipment, raw and in-process materials, etc.[20] These further analyses would make up a more fine-grained version of the Ishikawa diagram.

This discussion has considered the rationale for qualification, highlighting the role the qualification process plays in deviation investigations and RCA. Employee qualification proves to be a relatively expensive kind of training, when compared to training *per se*. The one-on-one character of this kind of training, the adding of a qualification event to the training process, and other factors contribute to this expense. How does an organization determine which procedures require employee qualification, and which require only training *per se*? This raises the issue of the criticality of a procedure.

8.5.1 Critical procedures require employee qualification

An important consideration in determining whether the training will consist of training *per se* or employee qualification is the criticality of the procedure and the process it represents. A procedure is considered to be critical, if:

- The procedure requires a complex or highly skilled activity or a job for which a high skill level must be demonstrated

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to perform a task in the direct manufacturing of a regulated product.

- The procedure addresses employee safety, or may result in a business compliance risk to the company if not properly performed.

These criteria clearly reflect aspects of criticality and complexity that go into risk assessment.

Whether or not a procedure is deemed to be critical should be guided by three basic questions. What might go wrong with the associated process? What is the likelihood that this will happen? What and how severe are the consequences if this goes wrong?[21]

8.6 Disqualification and requalification

Qualified employees can be disqualified for multiple reasons. These include time-based expiration of training, extended absences, job changes, and other understandable reasons. Disqualification can also occur should performance on the job fail to meet qualification standards. This disqualification process can be the result of a management or quality assurance (QA) department observation of non-compliant performance.

Disqualification can also be the result of a pattern of exceptions that can be attributed to the employee, such as the following:

- serious deviations;
- retraining history;
- repeated deviation;

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- investigation reports;
- out-of-specification results.

Management initiates the disqualification process. The QA department should review and approve any particular disqualification, as well as review and approve requalification standards and processes. The training department is responsible for monitoring disqualification and requalification events, as well as ensuring that the disqualification and requalification documents are submitted to the data entry personnel of the validated training tracking system or, in case of manual data processing, to the staff of the document repository.

8.7 Conclusion

While the FDA requires employees who work in controlled areas to be trained, it also provides latitude for organizations to develop their own training systems to make sure their employees are appropriately trained for GXP compliance. This chapter addressed key considerations in the topic of employee qualification, a critical kind of training in regulated industry. It further provided a comprehensive framework for an organizational approach to employee qualification. Concepts described in this framework should be incorporated in the organization's training policy and procedures addressing employee qualification. These concepts demonstrate an organized approach to employee qualification, compliant with regulatory requirements and expectations, and consistent with modern principles of risk analysis.

A typology of training, ranging from the least complex kind, awareness training, through training *per se* (which includes a KTA), employee qualification (training that

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includes an SDA), and finally up to the qualification of SMEs was presented. Specific groups emphasized in this discussion include employee qualification and SME qualification. Next addressed were specific employee qualification considerations, including employee qualification as process, qualification status, and measures to demonstrate qualification. Qualification may be demonstrated by use of a skills demonstration assessment checklist.

We then focused on the rationale for qualification; highlighting the role the qualification process plays in deviation investigations and RCA. Employee qualification proves to be a relatively expensive kind of training compared to training *per se*. How does management decide which procedures require employee qualification, and which require only training *per se*? We discussed the criteria for deciding what kind of training is appropriate for a specific procedure; this depends on the complexity and criticality of the procedure and the associated process. The final part delineated two other aspects of the qualification process, employee disqualification and employee requalification.

8.8 Notes

1. See 21CFR58.29(a), Personnel.
2. See John Levchuk (1990), now available as *Training for GMPs* (1991); also Vasilios Frankos (2007).
3. See FDA (2006) *Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations*. For other instances, see the following FDA Guidance for Industry (2003): *Current Good Manufacturing Practice for Medical Gases*; and FDA (2004) *Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice*.

4. An example of such awareness training is FDA ALERT Training initiative: "The ALERT initiative is intended to raise the awareness of state and local government agency and industry representatives regarding food defense issues and preparedness." Available from: *www.fda.gov/Food/FoodDefense/Training/ALERT/default.htm* There are no assessments.
5. For the business risk assessment (as contrasted to the quality risk assessment) that is involved in an organization's determination of due diligence, see the previous chapter.
6. See Edward E. Scannell (1992), "Facilitation; all but unknown a decade ago, 'facilitating' has become the 'in' thing for trainers. Many trainers, in fact, have abandoned their 'trainer' hats and term themselves 'facilitators' instead." An example is FDA FIRST initiative, which is closely related to the ALERT initiative. "Employees FIRST educate front-line food industry workers from farm to table about the risk of intentional food contamination and the actions they can take to identify and reduce these risks." Available from: *www.fda.gov/Food/FoodDefense/Training/ucm135038.htm* Ten "Knowledge Check Questions" are included at the end of the FIRST training materials.
7. E-learning is a special case of a communication or a training event. If the e-learning module lacks an assessment, it is a "page turner," hence awareness training on a par with a "read-and-sign" document. If the e-learning module includes an assessment, it is a training event, albeit special in the sense that it incorporates a virtual trainer.
8. There is a substantial legal exposure to the use of invalidated KTAs (short quizzes), and there are serious costs to validating KTAs; see Elizabeth Shoenfelt and

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L. Pedigo (2005); also see Christopher Smalley (2008) for further discussion of KTAs.

9. See, for example, Andrew Budson and Bruce Price (2005). They point out that the inferolateral temporal lobes are critical for the semantic memory system, the medial temporal lobes, including the hippocampus and parahippocampus, form the core of the episodic memory system, while the basal ganglia, cerebellum, and supplementary motor area are critical for procedural memory.
10. See Gerald McDonnell (2007); also see International Organization for Standardization (2000).
11. See Steven Ostrove (2008).
12. See Bohdan Ferenc (1999).
13. See FDA (2008) *Guidance for Industry, Process Validation: General Principles and Practices*, "Performance Qualification Approach."
14. As Christopher Smalley (2008) has put it:

> How does a new employee become educated in the skills needed to perform their job safely and effectively? Imagine for a moment that we are performing an IQ similar to that for a new piece of equipment. Are your specifications adequate? That is, are the job description and other documentation that describe the job to be performed adequate? What are the minimum requirements for the employee being 'installed'? op. cit., p. 519.

15. On the closely related notion of trainability testing, see Dominic Cooper *et al*. (2003); also Sylvia Downs (1985).
16. In a non-GMP framework, say OSHA, the performances are related elsewhere – say to the industrial safety of the employee.

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17. As Smalley (2008) has expressed it, "One of the best approaches to training on this content is to use the SME responsible for writing the procedures." op. cit., p. 520.
18. See 21 CFR 211.25(a), Personnel qualifications.
19. As Smalley (2008) has expressed it:

> "Let us recap some of the topics raised in implementing the 'IQ.' They are training requirements, training design, training execution, and evaluation of training. Embedded in these topics is the requirement to document," op. cit., p. 520.

20. The elements of auxiliary materials, for instance instruments and equipment, can be subjected to the same qualification process as the equipment element already discussed, even if they are used for training purposes only.
21. ICH (2005) *Quality Risk Management Q9*, p. 3. See FDA (2006) *Guidance for Industry, Q9 Quality Risk Management*, p. 3; and Sandy Weinberg and Ron Fuqua (2010). See also Kevin O'Donnell and Anne Greene (2006).

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9

Assessing trainee proficiency

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Abstract: This chapter will consider four components to the process of developing assessments of trainee proficiency. First, it reviews five dimensions of behavioral objectives: training audience; trainee performance; conditions for the performance; the measure of the performance; and criteria for successful performance, and the roles they play in the training module. Next, it considers the kinds of assessments that can be incorporated in a particular training module, ranging from assessments that approximate the core concept of a performance, through a series of increasingly distant surrogates, to an assessment based on the trainee's knowledge of the job, a KTA. Third, it sketches the preparation of several kinds of forms for assessing training, ranging across the continuum from work sampling, through SDAs, situational judgment tests, and finally to KTAs. Finally, it considers several issues that arise as we incorporate assessments into the training module: the timing of assessments, and ensuring the integrity of the assessment process.

Key words: conditions of performance, criteria for successful performance, individual training plan (ITP), knowledge transfer assessment (KTA), measure of performance, situational judgment test, skill demonstration assessment (SDA), testing security, trainee performance, training audience, training event, work sampling.

9.1 Introduction

Employees in regulated industries must be trained before they "touch" the product. According to the US Food and Drug Administration (FDA), each employee must have the "education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions."[1] This requirement has substantial implications for both managers and regulators. It also has substantial implications for the assessment of trainee proficiency.

Education and experience are dealt with differently than training. Education is typically documented in terms of grade level completed by – or diplomas awarded to – students in accredited institutions on the basis of a series of learning experiences over an extended period of time.[2] Experience typically refers to work experience, and is documented by the employee's length of time in a specific job position; often that is an extended period of time.[3] None of these measures is entirely adequate; in both work experience and education, the qualitative richness of the process is obscured by the measure of duration. But they provide guidance to corporate policy nonetheless.

The pharmaceutical or other regulated company seeks to ensure that employees have requisite educational attainment by effectively implementing recruitment policies or HR policies in support of continuing education. The company can either recruit employees who meet educational levels or can subsidize the employees' further education until they meet the desired level. Likewise, the company strives to ensure that employees have the requisite work experience. The company can either recruit employees who have specific work experience or can retain employees until they acquire the desired level of on-the-job experience.

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Training, by contrast, is typically documented in terms of specific training events in which the employee has participated. Management develops an individual training plan (ITP) for each job position, listing the various training modules that incumbents must complete.

The ITP and the associated training can be contrasted to the employees' educational attainment and work experience in several ways. First, the ITP tends to foreground short-term objectives rather than long term. Second, it tends to focus on enhancing employees' task performance on-the-job, rather than their more general knowledge and experience. Third, because of the longer time frames associated with educational attainment and work experience, these factors are taken as givens by management. Training, however, is widely seen as a corrective action for many problems. To the extent employees manifest performance gaps, those gaps will typically be remediated by training. Jack Gordon has pointed out that: "Managers send people to [training] courses precisely because they want to see observable behavior changes that will produce observable business results."[4]

So management's concern is with behavior change, which necessitates assessment of the effect of training on the trainee's task performance. Should training not correct the performance gap, the management will then turn to the more extreme measures of progressive discipline or discharge.

This concern is shared by regulators, who want to ascertain how well the organization's processes are in control. If there are problems in pharmaceutical manufacturing, let us say, the regulator wants to know how the organization responded to the problem. How was management notified? Was an investigation conducted, and if so, how well? How was the root cause identified? How was the corrective action

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formulated, and how was it executed? Many times the "cause" of the problem is identified as the residual category "human error," hardly a root cause at all. And then "re-training" is proposed as the "corrective action," as though the initial training could unexceptionably have been ineffective. Regarding auditors, as James Vesper has put it, "GMP auditors and regulatory inspectors are becoming more savvy about training and performance. They are asking to see evidence that the training was effective."[5]

Following the lead of management and regulators, we will focus in this chapter on the development of training assessments. There are four components to the process of developing assessments:

1. identifying the behavioral objectives of the training module, based on the relevant operational procedure and the Training Outline;
2. determining the kind of assessment to be used;
3. preparing the assessment materials; and
4. incorporating these assessment materials into the training module.

We will now examine the four components of the process of developing training assessments.

9.2 Behavioral objectives in the training module

Some rationale for behavioral objectives were mentioned in Chapter 4.[6] Behavioral objectives have several important functions. First, they permit intended training outcomes to be aligned with organizational objectives. Second, they permit trainees to have clear expectations

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of intended training outcomes. Third, they provide a sound basis for the design and development of training materials.[7]

Behavioral objectives have a number of dimensions.[8] Each must specify:

- the training audience;
- the trainee performance;
- conditions for the performance;
- the measure of the performance;
- criteria for successful performance.

Let us consider each of these dimensions in turn.

9.2.1 Training audience

The training audience is the set of job positions whose incumbents must receive training before they "touch" the product or, in the case of supervisors, before they supervise employees who will be touching the product.[9] All job positions that have responsibilities in a given standard operating procedure (SOP) are part of the training audience for that procedure. For example, by regulation, sanitization SOPs apply to contractors and temporary employees as well as to full-time employees.[10] As Roelof Kuipers has pointed out, it is important to define who needs what kind of training in a given organization. "With a large pool of electrical, mechanical and maintenance engineers, electricians, machine operators, contractors, and many more, not everyone needs the same skill set"[11]

The Boones have summarized this nicely: "Your behavioral objective should identify the specific audience you plan to target."[12]

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9.2.2 Trainee performance

Trainee performance is the set of behaviors that the trainee will demonstrate upon completing the training. In sanitization processes, regulations stipulate that employees must follow written SOPs.[13] An example of a behavioral objective that highlights observable performances is, "At the end of this training session, the trainee will be able to demonstrate the correct mopping technique for sanitizing controlled areas." This demonstration – this performance – will be observable to the trainer who will certify the performance took place; in principle, the performance would be observable to the trainee's manager or an auditor as well.

9.2.3 Conditions of performance

The conditions of performance is a list of conditions under which the trainee is expected to perform the behavior. For example, a behavioral objective might state: "At the end of this training session, the trainee will be able to demonstrate the correct mopping technique for sanitizing controlled areas, using the *double-bucket* process." The italicized text in the objective would be (part of) the conditions of the performance.

9.2.4 Measure of performance

The measure of the performance provides the categories or scale that represents the performance in qualitative or quantitative terms.[14] A measure of performance on a paper-and-pencil quiz could be the number of correct answers (perhaps compared to the total number of questions). The

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measure of sanitization of an area could be provided by environmental monitoring data. In James Popham's terms, it is a major shortcoming when: "behavioral objectives were not accompanied by assessment instruments specifically linked to those objectives." He continues that learning objectives: "will have little effect on day-to-day instruction if not accompanied by relevant assessment devices.[15]

FDA regulations stipulate that "A protocol is required to contain . . . A description of the observations and measurements to be made to fulfill the objectives of the study."[16]

9.2.5 Performance criteria

Finally, criteria for performance specify the limits of successful performance. For instance, many times, the performance on a paper-and-pencil quiz is considered successful when 80% of the responses are correct. Again, the sanitization of an area has been successful when environmental monitoring data for each room after sanitizing is within acceptable limits. The inclusion of criteria is important because it highlights that the behavioral objectives are built into the assessment measures. As Jack Gordon (ibid.) has put it, "When you know what targets you're shooting at, keeping score becomes much easier."

In this section we have considered the five dimensions of behavioral objectives – training audience, trainee performance, conditions for the performance, the measure of the performance, and criteria for successful performance – and the role they play in providing focus to the training module. Given the behavioral objectives and their associated measures and criteria, the kind of assessment can be specified.

9.3 Which kind of assessment

At a very general level, training involves two components – a Training Event, followed by a Performance that demonstrates whether the training had (or did not have) the desired impact on the job, in the workplace.[17]

The Training Event might be a structured on-the-job training (SOJT) event; it might be a classroom event; it might be an e-learning event. The Performance might be the SOJT trainee's independent execution of the relevant tasks; it might be the trainee's accurate logbook entry following a classroom session; it might be the trainee's completion of a quiz at the end of an on-line session with 80% of the responses correct. Of course, the performance might be unsuccessful – the trainee might fail to execute the relevant tasks, might make an inaccurate logbook entry, might score less than 80% on the quiz.

The Training Event is a set of independent variables (the predictors); the associated Performance is a set of dependent variables (the criteria). Both components – the Training Event and the Performance – are multi-dimensional.[18]

The Training Event includes trainer(s), trainee(s) with skill set(s) and disposition(s), training organization (supervisory factors, business case), training facilities (allocated space, allotted time, utilities), and training materials (instruments and equipment, raw and in-process materials).[19] Training materials also include the training script – for a typical SOJT event, for instance, the script would spell out in some detail the steps in the Prepare, Tell, Show, Do, and Follow-up cycle to be followed in this event.[20]

The Performance component (continuing with the SOJT illustration) includes the trainee's independent and satisfactory performance of the relevant tasks in a real work setting, as judged by a supervisor or as indicated on some

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business process metric. The Performance component usually has both individual level and group level (work team) elements. There is a feedback loop between the performance and the training event. As we observed before, it is possible that the task performance by the trainee was unsuccessful. In that case, the adequacy of the trainers' ability or preparation, the suitability of the training materials, the capability or motivation of the trainee, as well as the timing or situation of the training event (or a combination of these) can be called to account.

The core concepts of Performance are as follows:

- a real work setting; wherein
- a trainee engages in a training-related task; and
- the task is completed, either successfully or unsuccessfully.[21]

This concept of Performance is not always logistically feasible. Which tasks in a specific process must be completed? How can a real work setting – with all the demands of production and output – be accessed for training purposes? These are difficult questions to answer, difficult enough that it is frequently necessary to use proxies for purposes of training assessment.

Whether core concepts of Performance or their proxies are utilized in assessment of training, they must be documented in procedures, protocols, and SOPs. An SOP stipulates the standards for the core concepts of Performance or for the proxies.

Turning first to the core concepts "real work setting" and "training-related task," if that setting is unavailable for task samples, or the task itself is inaccessible, a surrogate measure must suffice. Brinkerhoff gives the example of training on cardiopulmonary resuscitation (CPR) techniques: "Barring a workplace heart attack, we would find no on-the-job application of the skill learned."[22]

The surrogate in such a case is a Skill Demonstration Assessment (SDA), where the trainee independently performs the task(s) on relevant equipment outside of the real work setting – off-hours, on placebo batches, during production shutdowns, etc.

Turning next to the core concept "task completion," there are situations where the process cannot be broken into discrete tasks, or is for some reason inaccessible. Consider, for example, equipment that has a biennial preventive maintenance schedule. That equipment may not be available for the training of mechanics for more than a year. In such a case, another kind of proxy must suffice. That is a Knowledge Transfer Assessment (KTA). A KTA is a paper-and-pencil test that predicts performance on-the-job. If task completion or non-completion can be correlated with a test score, so that high scores correlate with task completion and low scores correlate with non-completion, then the KTA is validated, and performance on-the-job can be predicted from trainee performance on the KTA.[23]

If the KTA has not been validated, it can still prove useful as an interactive element within the courseware itself. It can take the form of "study questions," providing guidance to trainers as they interact with trainees in facilitating the course. Perhaps, needless to say, in this form the questions are not part of any assessment.

We have not included Donald Kirkpatrick's Level l, the "trainee reaction" measure,[24] in our list of assessments for several reasons. First, there is no evidence that a trainee's appreciation of – or affective response to – a training event correlates with the trainee's task performance.[25] Thus the trainee reaction is not a surrogate for performance. Second, if an assessment of the utility of the training content or materials is needed, a review of the module during the pilot implementation, by the training and development peers, will

likely provide a more focused and accurate assessment than the reactions of the trainees. Third, the use of trainee reactions raises the possibility of documented negative judgments. For instance, suppose the trainee reaction form uses a question such as "What can be done to improve this training module (or training event)." What shall be the corrective action of the trainer to negative judgments? A regulator may come across these documents during an audit, and can rightly ask about the remediation that followed from them. Better these judgments were not documented in the first place, if there was no intention to take corrective action.

In this section we reviewed several kinds of assessments that can be considered for incorporating in a particular training module. These range from assessments that approximate the core concept of a Performance, through a series of increasingly distant proxies, to an assessment based on the trainee's knowledge of the job, as reflected in a validated KTA.

9.4 Preparing the assessment materials

Once the kind of assessment has been selected, the assessment materials can be prepared. The first step in preparing assessment materials is to complete a task analysis. Once the task analysis has been completed, the specific tasks and subtasks will be listed, groups of tasks will be aggregated or "chunked," the flow of the process will be indicated, and concepts providing the "science" for task performance will have been associated with each chunk.

This completed task analysis will include an extensive set of tasks. The second step is to winnow through the particular

tasks whereby the trainee's performance will be assessed. One way would be to take a representative or random sample of the set of tasks. Another would be to take a purposive sample of those tasks that are judged critical to the whole process.

Once the list of tasks is a manageable length, this becomes the work sample for assessment. The third step is to prepare a protocol for the assessment, indicating that the trainee is expected to perform the listed tasks under specified conditions, and meeting certain criteria for success. As Vivian Bringslimark has expressed it:

> Using an approved [operational] SOP, a qualified observer or trainer should observe the employee performing the [operational] procedure, compare the performance to the [operational] SOP, and record the results on a qualification or competency assessment sheet. The results should be communicated to the employee, his or her supervisor, and to the trainer responsible for the original training, indicating whether the prescribed level of competency has been attained.[26]

As we have noted above, there are circumstances where task sampling is not practicable, and a surrogate is necessary for assessment. That surrogate is the SDA. A training procedure stipulates how, when, and where the trainee can independently perform the task on relevant equipment outside of the real work setting. As Bringslimark has put it, the process of how the assessment sheets are approved, distributed, and evaluated also should be defined in that (training) SOP as part of the overall training system. We will briefly describe that process.[27]

The originator uses the number and version of the relevant operational SOP as the course number and version for the SDA form. The form includes a number of yes/no statements.

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	Yes	No
1. Use of appropriate GMP requirements that relate to the defined process.		
2. Use of adult learning practices and principles during the training.		
3. Demonstration of effective delivery skills for the training session.		
4. Use of behavioral objectives.		
5. Demonstration of appropriate interaction with audience.		

Figure 9.1 **Illustrative SDA items from GMP train-the-trainer program**

These describe the identified critical or representative tasks to be assessed on the SDA. These are the items assessing the trainee's performance, as illustrated in Figure 9.1.

The trainee performs, and the trainer or some other subject matter expert (SME) monitors the performance and checks each item in turn: "yes" if the performance was successful, "no" if not. When the performance is complete (whether successful or not), the trainee and the trainer sign and date the SDA. Area management may sign as well. The completed form is submitted to the data entry personnel of the validated training tracking system or, in case of manual data processing, to the staff of the document repository.

If SDAs are not available, situational judgment testing can be a proxy. In a typical situational judgment test, trainees are presented with a variety of situations (or scenarios) they might encounter in the workplace. Most situational judgment tests take a paper-and-pencil form, although they could take an on-line form. These situations are usually established on the basis of a job or task analysis. The trainee selects the

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best way to handle each situation. The trainee's choice is compared to a response called "correct." The "correct" response is established either empirically or by the collective judgment of a panel of SMEs.[28]

Should situational judgment testing not be a feasible alternative, a job knowledge test can be a surrogate. A KTA is a paper-and-pencil test that predicts performance on-the-job. The items in the KTA can be constructed either (a) out of material contained in training courses, user manuals, technical handbooks, etc., or (b) from material provided by a panel of SMEs; in either case the material reflects the content of the job. The items that should be selected are the best discriminators between employees who are judged more proficient and less proficient performing the task. Thus high scores correlate with proficiency and low scores correlate with less proficiency; the KTA is validated, and performance on-the-job can be predicted from trainee performance on the KTA.

In this section we have sketched out the preparation of several forms for assessing training, ranging across the continuum from work sampling, through SDAs, situational judgment tests, and finally to KTAs. Once the assessment forms have been prepared, they can be incorporated into the training module.

9.5 Incorporating assessments into the training module

Assessments can be incorporated into a training module in several ways: as a pre-training assessment, as a post-training assessment, and interspersed throughout the training material.[29]

Pre-training assessments (pre-tests, sometimes called "knowledge checks") are administered before the training begins. These assessments can take the form of task samples, SDAs or KTAs. If they have been administered before the trainees congregate at the training site, the trainer can compile the scores, which may allow the trainer to adapt the training materials to the specific levels of trainee preparedness.

Post-training assessments (post-tests) are administered after the training has been completed. Again, they can take many forms. They can be administered before the trainees leave the training site, or they can be administered at a later date, or both. If the post-tests are administered while the trainees are still on-site, and then at one or more later times, they can serve as measures of the sustainability of the training as well as the effects of the training. Tennant, et al. (ibid) suggest three kinds of post-training assessments: an "immediate test," to be carried out when the training has been completed, an "intermediate test" when the trainee has returned to the job, and an "ultimate test" to be employed "after an appropriate time has elapsed in order to measure the improvement of the skills, and behavioral changes."

Post-test scores can also be compared to pre-test scores. Given equivalent forms, differences in scores can be taken as some evidence of training effects.

Finally, depending on how the work process has been chunked and conceptualized, assessments can be incorporated throughout the training material, in addition to any other assessments that are used as pre- or post-tests. Assessments throughout the material serve to reinforce training at a more fine-grained level, to break up training material into lengths closer to adult attention span, etc.

Not only is the timing of assessments critical, but the security of the assessment process is critical as well.

9.5.1 Test security

Assessment of training can place trainees under considerable personal and organizational pressure to succeed.[30] In addition, valid assessment forms can be quite costly to develop.

Therefore, attention must be paid to ensuring test security – that is ensuring that the training event and associated performance are secure in terms of the five dimensions of the behavioral objectives listed above. The performance must be identifiably that of the individual trainee, under the stipulated conditions, and demonstrably successful (or not). These security issues have been highlighted by the increasingly widespread use of on-line testing and assessment.[31] The security issues have much longer history, of course, as a review of test security problems involving home-schooled children makes clear.[32]

There are several approaches to test security for assessment of training. These include verifying the identity of the trainees, and monitoring the assessments. These approaches are familiar to those of us who work in regulated industry, and should be stipulated in an appropriate training SOP.[33] Verifying the identities of users (trainees) in the case of on-line testing and assessment means being Part 11 compliant.[34] Monitoring the assessment of training means having the task defined in the Action column, and the responsibility for that task listed in the Responsibilities column of the relevant operational SOP.[35]

In this section we have commented on several issues that arise as we incorporate assessments into the training module. These include the timing of assessments – whether to conduct assessments before, during, or after the training event – as well as how to ensure the integrity of the assessment process.

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9.6 Conclusion

In this chapter, we focused our attention on the development of trainee assessments. We identified four components to the process of developing assessments. First, we reviewed five dimensions of behavioral objectives – training audience, trainee performance, conditions for the performance, the measure of the performance, and criteria for successful performance – and the role they play in providing focus to the training module. Next, we examined the kinds of assessments that can be incorporated in a particular training module, ranging from assessments that approximate the core concept of a performance, through a series of increasingly distant surrogates, to an assessment based on the trainee's knowledge of the job, a KTA. Third, we outlined the preparation of several kinds of forms for assessing training, ranging across the continuum from work sampling, through SDAs, situational judgment tests, and finally to KTAs. Fourth, we commented on several issues that arise as we incorporate assessments into the training module, including the timing of assessments as well as how to ensure the integrity of the assessment process.

After the training materials and assessment materials have been developed, the training module can be implemented, and the module can be evaluated.

9.7 Notes

1. Thus for pharmaceuticals – see 21 CFR 211.25; for non-clinical lab personnel, 21 CFR 58.29; for biopharm personnel, 21 CFR 600.10; for medical device personnel, 21 CFR 820.25; for human tissue recovery personnel, 21 CFR 1271.170.

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2. See David Jaeger (1997).
3. See Paul Tesluk and R. Jacobs (1998), esp. page 324: "work experience has been used almost interchangeably with tenure and seniority."
4. See Jack Gordon (2007).
5. See James Vesper (2001).
6. This was discussed in Chapter 5.
7. See Clifton Campbell (2000); also Clifton Campbell (1999).
8. See Harry and Deborah Boone (2005).
9. See 21CFR 211.25 (b), "Personnel Qualifications."
10. See 21 CFR 211.56 (d), "Sanitation."
11. See Roelof Kuipers (2004).
12. See Boone and Boone, ibid.
13. See 21 CFR 211.56 (b), "Sanitation" for Facilities; 21 CFR 211.67 (b), "Equipment Cleaning and Maintenance."
14. See David Merrill (2006).
15. See James Popham (2001).
16. See CFR 312.23 (a)(6)(iii)(f) This is true of the study of training no less than clinical trials.
17. It may be too strong to state that a Training Event "causes" a Performance; perhaps we should say Training Events "influence" Performances. An important part of evaluating training programs consists of determining how substantial that "influence" is. But evaluating programs comes later; for now it is crucial to keep in mind that the assessment of training involves performances by an individual or a group (work team). On the topic of evaluation, see also Kaye Alvarez, E. Salas, and C M. Garofano (2004).
18. The Training Event/Performance model is overly general. Between the set of independent variables and the set of dependent variables is a set of intervening variables. These intervening variables include cognitive,

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conative, and affective factors that impact the transfer of training to the workplace. See also David Chan (2005).

19. The organization and its environment – within which the Training Event, training organization and training facilities are located – are also important for situating employees and their tasks. These two categories can have a profound impact on the conduct and effectiveness of training.
20. See also Paul Lyons (2005).
21. See Militza Callinan and Ivan Robertson (2000). See also C.L. Brisley (1952).
22. See Robert Brinkerhoff (1988).
23. It is worth repeating that there are substantial legal implications to the use of non-validated tests in employment-related situations; see US Department of Labor (2000).
24. See Donald Kirkpatrick (1994).
25. See George Alliger *et al*. (1997).
26. See Vivian Bringslimark (2004), esp. p. 49.
27. See Bringslimark, ibid.
28. See Michael McDaniel and N.T. Nguyen (2001); also Michael McDaniel, F. P. Margeson, E.B. Finnegan, MA. Campion, and E.P. Braverman (2001).
29. Charles Tennant, M. Boonkrong, and P Roberts (2002) have stressed the significance of the timing of assessments in training, esp. page 237.
30. This is a broader social issue; see Carolyn Kleiner and M. Lord (1999).
31. See Neil Rowe (2004).
32. See Richard Mueller and D. Brunetti (1989).
33. See James Vesper (2000).
34. See 21 CFR 11.10, "Controls for Closed Systems," and 21 CFR 11.30, "Controls for Open Systems."

35. See also Paul B. Roberts (2006); also Dinah Gould, Daniel Kelly, Isabel White, and Jayne Chidgey (2004); and Dinah Gould, Daniel Kelly, and Isabel White (2004).

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10

Pilot implementation

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Abstract: Pilot testing of a program – including training programs – can add considerable value for an organization, by contributing to program improvement. While a training program – for example, training module, organizational development program, LMS courseware – is still in the developmental process, not yet approved for final rollout, a pilot can provide significant data about the real-world impact of the product, going well beyond the data that can be inferred from the material that appears on the storyboard. The data derived from the pilot can be used to revise and improve the training module before it is rolled out to the department, site, or entire workforce. This will of course add to the overall cost of module development, but it is a cost that is well worth incurring. We review the role of a pilot implementation in the process of developing a training program, looking initially at strategic issues and then reviewing some tactical issues. First, we consider the relationship between a pilot and the program improvement design and development model. Next, we compare pilot implementation to other pilot projects in the pharmaceutical industry. Then, we consider a number of conditions that will facilitate or inhibit the implementation of a training program. Turning to tactical issues, we review how an instructional designer prepares for a pilot implementation

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of a training program, conducts a pilot implementation, and finally, evaluates a pilot implementation.

Key words: disappearing training intervention, facilitating conditions, feedback, obstacles to implementation, pilot implementation, pilot project, program improvement, scale up, shifting training audience, variable implementation.

10.1 Pilot implementation and the program improvement model

There appears to be some confusion about the meaning of the term "Implement."[1] We hear that the "Implementation" phase means that the training module is developed, finalized, and ready to be rolled out. However, this viewpoint gives rise to two questions. First, what then are we to make of the "Evaluation" phase that comes after the Implementation phase? Is this to be only a summative evaluation? Does this mean that there is no place in the program improvement model for formative evaluation?[2] That would be an unduly restrictive view of this model of program improvement.

Second, the program improvement model is an iterative feedback model, which means that the results of the Evaluation phase are fed back, closing the loop, facilitating further refinement of the training program. If the evaluation shows that the module has shortcomings, such as lacking clarity, those shortcomings are fed back to the author(s) to be analyzed again. Further design and development efforts follow until the module meets the organization's needs and standards. That feature of the model – iterative feedback – strongly suggests that the Implementation phase cannot simply be the finalized rollout of the training program.

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Indeed, the Implementation phase of the program improvement model includes pilot implementation as well as final implementation.[3] As Gillis and Beauchemin have put it, "The term 'pilot' warns everyone to expect some adjustments. [. . .] Revisions and modifications make even the best training programs more effective, and evaluating the pilot reveals potential program improvements."[4] The notion that the phase is a "pilot" of the training program, rather than a finalized rollout, highlights the iterative feature of the model.

Thus the program improvement model should be conceptualized as having two paths out of the "Development" phase. One path leads to pilot implementation, followed by formative evaluation, from which a feedback loop allows further analysis, design, and development. At some point, determined by management, the training program is judged to be ready for the other path. It then moves to final implementation, followed by summative evaluation (Figure 5.2, above). In this chapter we will focus on the place of pilot implementations in program improvement.

10.2 Pilot projects in the pharmaceutical industry

In the pharmaceutical industry we have a well-known example of a pilot activity that illuminates the relationship between the (Pilot) Implementation phase and the rest of the program improvement model. That is the transition between laboratory research and development, and commercial manufacturing.

When a pharmaceutical company has discovered a promising product in the R&D laboratory, it goes into a development phase. The company subjects the product to clinical trials to determine its safety and efficacy. If it is

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deemed safe and efficacious, it is a candidate for commercial manufacture and marketing. The question is: how does the company move from the scale of laboratory production, perhaps several ounces of product in total, to the commercial scale of thousands or millions of units of product? This is where the pilot project fits in.[5]

The company pilots the manufacture of the product, as a transition from the laboratory scale to the commercial scale. The pilot has a number of outcomes, four of which are particularly important:

1. It demonstrates the feasibility of the scale-up in general.
2. It demonstrates the validity and reliability of the particular process selected for the pilot.
3. It generates parametric product and process data for commercial manufacturing.
4. It provides data for budgeting, planning, and scheduling of subsequent manufacturing.

Each of these outcomes may prove positive or negative for the future of the product. As examples of negative outcomes: the scale-up process may not prove technically feasible, the particular process may be unreliable, there may be off-spec findings during scale-up, and the process may not be economically feasible.

The relationship between the (Pilot) Implementation phase and the rest of the program improvement model is similar. When a pharmaceutical company has discovered a promising solution to a training gap, it goes into a development phase. The company assigns an instructional design team to take the promising solution and develop it into a draft training module. If the training module seems to be efficacious, in terms of face validity and peer review, for example, it becomes a candidate for department-wide, site-wide, or even

corporate-wide rollout. The question is: how will the company move from the instructional designer's desktop and story board to the whole workforce? This is where the pilot implementation fits in.

The company pilots the training module, as a transition to the entire workforce. The pilot has several outcomes. It shows whether or not the promising solution can be scaled up in general. The pilot shows the validity and reliability of the specific interpersonal and institutional process selected for the pilot (or perhaps it shows unreliability). It generates process and outcome data that may be important for the finalized training program. And it provides data on cost and scheduling considerations that should be taken into account in the wider rollout.

There are two basic possibilities for the pilot implementation of a training program, depending upon two kinds of participants in the pilot. These participants involve end users on the one hand, and training and development peers on the other. End-user testing intends to assess how representatives of the target audience interface with the training program that has been developed for them. The peer inspection subjects the training program to a review for consistency with design standards and program logic;[6] it also can identify problems such as repetition, overtaxing of memory, etc.

These two possibilities may disclose different kinds of problems with the training program. End-user testing can find problems that are overlooked by peer inspection; likewise, peer inspection methods can find problems that are overlooked by user testing. In many cases, the best results can often be achieved by combining the two approaches.[7]

This section has compared pilot implementation of a training module to other pilot projects in the pharmaceutical industry. The next section will consider the conditions that facilitate that implementation.

10.3 Conditions facilitating implementation

There are specific conditions that facilitate the pilot implementation, and eventual rollout, of a training program. The absence of these conditions can inhibit the implementation and rollout. We should ensure that these conditions are present for our pilot implementation.

Donald P. Ely has discussed eight conditions that facilitate pilot implementation.[8] There must be the following:

1. a dissatisfaction with the *status quo* – things could be better;
2. sufficient knowledge and skills on the part of those who would implement the training program;
3. adequate resources;
4. time – as Ely puts it: "Good time; Company time; Paid time;"
5. rewards or incentives for participants;
6. the expectation and encouragement of participation in decision-making about the implementation;
7. commitment by those who are involved;
8. evident leadership.

Ely points out that this list of conditions has been validated, and can be used to develop a checklist for the implementation project. But, he cautions, these conditions must not be viewed as formulas or rules; they should be subject to local conditions.

Moreover, there can be a profound political aspect – either pro or con – to an implementation effort. As Carol Weiss has expressed it, "This is because policies and programs are proposed, defined, debated, enacted, and funded through

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political processes, and in implementation they remain subject to pressures both supportive and hostile."[9]

This section presented a number of conditions that will facilitate the pilot implementation of a training module. The next section addresses various obstacles to that implementation.

10.4 Obstacles to implementation

There is also a series of obstacles to implementation. ABT Associates has identified a number of these.[10] The following three obstacles are of particular interest to us:

1. disappearing training intervention;
2. variable implementation;
3. shifting training audience.

10.4.1 Disappearing training intervention

The training intervention is the trainer's execution of a script.[11] This script is executed (or performed) by the trainer(s) in specified training facilities, within allocated space and allotted time, and employing requisite training materials. It is performed for a specific audience, a specific group of trainees. The training intervention disappears when the trainer fails – for any number of reasons – to perform the script within that space and time, for those trainees. The trainer might not be proficient in performing the script, resulting in a clumsy performance; the trainer might not have physical access to the script, resulting in an impromptu performance; the trainees might be inattentive or asleep, etc. In any case, should the training intervention disappear, there

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is no predictor of interest for the subsequent trainee performance.[12]

10.4.2 Variable implementation

The trainer performance of the script must be relatively standardized across trainers, facilities, times, and trainees. The word "standardized" is critical here: standardization implies standards, or criteria for the performance. The training intervention becomes (unacceptably) variable when the performance deviates from those standards. On the one hand, the criteria will be set by management; on the other hand, the trainer's preparation must include an assessment of the relevant scripted tasks, as judged by a supervisor or as indicated on some business-process metric. In the case of team-led training events, it will include both individual level and group level (training team) elements. In the absence of such standards and criteria, as Beth Gamse *et al*. have pointed out, "if no impact were to be found, it would be impossible to know if it was because of a failure of implementation, a failure of [the training design], or both."[13]

10.4.3 Shifting training audience

There are obstacles to implementation on the trainee side as well. Employees are transferred or reassigned and are no longer part of the training audience. Curriculums and individual training plans (ITPs) change and the training is no longer relevant to the employee's work assignments. This attrition and change has an obvious effect on implementation of training modules and the assessment of sustainability of training. Beth Gamse *et al*. have commented that it is not so much "that such changes create a bias between groups;"

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they go on that what is especially "problematic is that the changes create noise or unknown variation against which it is difficult to detect [program] impact."[14]

These three obstacles are listed in order of increasing seriousness. The disappearance of the training intervention can be addressed and perhaps controlled by a suitable train-the-trainer (TTT) program, a remediation that is within the scope of the Training Department. Likewise the variability of implementation can be remedied by well-known quality control measures, which are within the scope of the Quality Assurance Department. The problem of shifting training audiences is less tractable, since it is directly caused by the business needs of the organization.

With those strategic considerations in mind, let us turn to some tactical issues. Based on our own experience with pilot projects, we will review how to prepare for, conduct, and evaluate a pilot implementation.

10.5 Preparing for a pilot implementation

Preparing for a pilot implementation has seven steps.

10.5.1 Step 1: Review relevant material

Review all relevant material that has been developed so far, including any pertinent standard operating procedures (SOPs), the training materials (including the training script), the trainee assessment materials, and the evaluation materials. It is important to distinguish between trainee assessments that measure the trainee skill acquisition, and the evaluation measures of the training module's adequacy in

terms of some set of institutional standards. Just as the organizational or institutional purpose of a training module should not be confused with its behavioral objectives, so evaluation should not be confused with assessment. The two are, of course, related – trainee success will contribute to program adequacy – but the two are, nonetheless, distinct.

10.5.2 Step 2: Prepare an execution plan

Next, prepare a plan for the pilot, sometimes called an Execution Plan. We can turn to the Training Outline for a brief overview of the module. As discussed in Chapter 5, this is the brief, one- or two-page outline that lists the name and course number of the module, identifies the training audience, indicates how the module fits in the larger curriculum, lists the behavioral objectives, indicates the delivery modality, the anticipated duration of the training session, identifies the assessment materials, etc. In addition to the information derived from the Training Outline, the plan should sketch the various roles and responsibilities for the preparation, execution, and evaluation of the pilot implementation. This plan will indicate the extent to which end-user testing, and peer inspection, will be involved. Once the plan is ready, it is important to get management approval of the plan for the pilot.

10.5.3 Step 3: Prepare checklist for pilot

As with any well-planned training event, it is hard to imagine too much detail in the checklist for the pilot implementation. Better the checklist should be overly detailed than to realize at the last minute, with the participants coming in the door,

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that we have neglected some critical factor. Once we have developed a comprehensive checklist, this can provide a template for subsequent pilots.

10.5.4 Step 4: Schedule facilities

Next, schedule room(s) in the case of classroom training, or work station(s) and equipment in the case of structured on-the-job training (SOJT) sessions. When scheduling, try to get the same room, work station, or equipment that would be used in any other training event.

10.5.5 Step 5: Prepare required materials

Prepare all required materials for the pilot session, including training materials, safety materials, and process materials. These materials can be listed on the comprehensive checklist, and can be ignored (N/A'd) if not needed.

Training materials include:

- flip charts and markers;
- handouts for trainees;
- job aids;
- placards;
- PowerPoint slides;
- script for trainers;
- transparencies;
- white board and markers.

Safety materials include:

- Job Safety Analysis (JSA);
- Material Safety Data Sheet (MSDS);

- Personal Protective Equipment (PPE).

Process materials include:

- equipment;
- controls (make sure the switches work, etc.);
- instruments;
- utilities (make sure the water runs when you open the tap, etc.).

10.5.6 Step 6: Review list of invitees

Review the set of end-users, the target audience for the training program. Who is in the scope of this training? Ensure coverage of all significant groups within the scope.[15] This means including differing technical skill levels; different cultural, language, and ethnic groups; different sites and facilities; differing tenures – some new hires, some old timers, etc. It is important to estimate the percentage of invitees that will actually be attendees; that estimate will ensure you have enough participants attending the pilot to provide reliable and credible data on outcomes and process. The estimate of invitees who will actually attend will depend upon your experience, or the experience of your training and development peers. Then you can assemble the list of invitees, and again be sure to get management approval. Each attendee's manager will need to approve participation.

10.5.7 Step 7: Send invitations

The final preparatory step is to send invitations to the pilot session. Invitations should be sent to each participant

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(trainee), as well as to your training and development peers. Inviting your peers is a courteous collegial gesture, and these attendees can provide peer evaluations of the session that the participants may not be prepared to do. The invitation should include a brief overview of the module indicating that this is a pilot; be sure to mention that training credit in the employee training history will depend on extent of revisions that are required. If minor revisions are called for, training credit can be given for the session. If major revisions are needed, attendance can be noted but credit cannot be given, since the revised module that will ultimately be rolled out will not be the same as the pilot module.

10.6 Conducting a pilot implementation

Conducting a pilot implementation has eight steps.

10.6.1 Step 1: Check the checklist

When the day and time of the pilot session arrive, use your checklist to make sure that everything is in place and ready to go. Welcome the end-user trainees and your training and development peers. Indicate again that this is a pilot implementation; repeat that credit to the participants' ITPs will depend upon the extent of revisions that are needed. Even if credit cannot be given because major revisions are called for, the trainees' participation in the development of this module will be noted and appreciated. Discuss the logistics of this facility, where the water fountains, coffee machines, and restrooms are located, etc. Point out relevant Emergency Response Plans, fire escape routes, etc.[16]

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10.6.2 Step 2: Distribute training materials

Distribute the training materials to the attendees, and indicate criteria for success – 80%, 100%, or whatever. The preliminary knowledge check, if applicable, should then be administered.

10.6.3 Step 3: Provide overview of training module

Now is the time to explain the content of the pilot module. This is an opportunity to present the "science" of the process; it is more than a sequence of tasks. Present the behavioral objectives for the module. It is worth repeating that adults learn best when they have crystal clear expectations about their projects; hence we always use behavioral objectives. Invite questions or concerns from the participants (trainees), and specify the feedback process. Stress that you welcome feedback; that the main purpose of a pilot implementation is to elicit feedback for program improvement. Specify how the participants should make their feedback – whether they should interact immediately with the trainer(s) when they have an issue, or they should note the issue for later discussion. In either case, every issue should be recorded for later attention. Also, mention that they will be called upon to evaluate the pilot session before they leave – we will return to this point in Section 10.7.

10.6.4 Step 4: Explain each task of training module

Move through the module, section by section, task by task. For each section and task, discuss the purpose of the task;

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the importance of the task; when and where to perform the activity; and the expected results of correct performance and the potential results of incorrect performance. Highlight critical safety points for each task (as needed); also highlight key cGMP points for each task (as needed). Then invite questions or concerns. It perhaps goes without saying that training and development peers should hold their questions and concerns for a post-session debriefing. It can be quite disruptive if the peers raise questions while the trainees are present. On the one hand, the trainees can be confused by the different "spins" on the training material. Moreover, the exchange between training and development peers can suggest that there is dissention within the training unit.

10.6.5 Step 5: Demonstrate each task (as needed)

This step is particularly important in SOJT sessions. Also in SOJT sessions, allow the trainee to practice; record the trainee's progress through the sequence of tasks. It is important to track trainee progress on an explicitly non-GMP progress form. Since trainee progress will only be on part of the module – representing part of a SOP – that progress cannot be recorded on a controlled (GMP) form. The non-GMP progress form can be discarded after the module is completed, after the session is duly recorded on a controlled training tracking form.

While the trainees are progressing through the sequence of tasks, provide assistance as needed – while the trainee prepares for independent performance (for SOJT), and while the trainee prepares for an assessment (for a classroom module).

10.6.6 Step 6: Trainees perform OJT tasks

In the case of SOJT, allow independent performance by the trainee. Observe that the trainee performs each task safely, correctly, and without any coaching from the trainer.

10.6.7 Step 7: Assess performance

When the independent performance is completed, or when the classroom session is completed, assess each trainee's performance. Utilize the appropriate GMP assessment form, and assess independent performance (for SOJT); assess knowledge transfer (for a classroom module).

10.6.8 Step 8: Complete all records

The final step in conducting the pilot session is to record the completion of the module. Use the training tracking form, which as we have noted is a GMP form.

Once the pilot session is completed, it is time to evaluate the adequacy of the training module, propose revisions as needed, and prepare a report to management.

10.7 Evaluating a pilot implementation

Evaluating a pilot implementation has six steps.

10.7.1 Step 1: Ask trainees to evaluate the pilot module

Explain the evaluation process, and how the evaluations will be used in feedback for program improvement. Use explicitly

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non-GMP evaluation forms. Since at this point we are evaluating a work in progress, the training module that is under development, not yet approved – there should be no record of that progress on a controlled (GMP) form. Sometimes "sticky notes" – clearly not controlled documents, can be used to record the trainees' evaluations. The non-GMP evaluation forms can be discarded after the module is completed and approved. Collect the evaluations from the trainees as they depart the room.

10.7.2 Step 2: Ask peers to evaluate the pilot module

The second step is to collect evaluations of the session and the module from your training and development peers. This can be done by a face-to-face debriefing or, again, by the use of an explicitly non-GMP evaluation form.

10.7.3 Step 3: Review all evaluations

The third step is to review all the evaluations of the module and the pilot session.

10.7.4 Step 4: Prepare evaluation report

Prepare an evaluation report summarizing the evaluations; consider making revisions to the training program. Propose needed revisions to the module, and get management approval of these revisions. As Gillis and Beauchemin have put it, "Revisions may include incorporating new material to help the program meet its objectives or changing the objectives themselves based on trainees' or managers' input. Changes must support specific, measurable objectives."[17] In

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light of the seriousness of the needed revisions, determine the appropriate training credit for participants.

10.7.5 Step 5: Discard all non-GMP evaluation forms.

10.7.6 Step 6: Submit all records and reports

The last step is to submit the training tracking form for appropriate credit to each participant's ITP.

10.8 Conclusion

The well-executed pilot implementation of a training program can add considerable value for an organization, providing significant data about the real-world impact of the product. This data can go well beyond what can be inferred from the material that appears on the story board. The data from the pilot implementation can be used to revise and improve the training program – as part of a formative evaluation – before it is finalized and rolled out.

10.9 Notes

1. There are some slight variations in the terms applied to the phases of the program improvement model. For instance, with reference to medical devices, the FDA has used the term "establish" to encompass three of the phases, "define," "document," and "implement;" see

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21 CFR 820.3(k). Similarly, critics of the ADDIE model occasionally refer to the implementation phase as the "Instruct" phase of the model. See Jack Gordon and Ron Zemke (2000).

2. See Michael Scriven (1996).
3. On the complexity of the Implementation phase, see James Mosley and Nancy Hastings (2000). Irene Visscher-Voerman and Kent Gustafson (2004) distinguish "implementation anticipation" (what is usually called Pilot Implementation) and "implementation" proper.
4. See Marge Gillis and Katherine Beauchemin (2000); see also David Gallup, K. Beauchemin, and M. Gillis (1999) on "Implementation." See J. Lynne Brown and N. Kiernan (2001); and J. Lynne Brown and N. Kiernan (1998).
5. See Douglas Watson *et al.* (2001); also P. Lendren *et al.* (2001).
6. On program logic and the Logical Framework Approach (Logframe) to training program design, see Des Gasper (1999); also H. Eggers (1998).
7. See Jakob Nielsen (1994); also J. Nielsen (1999).
8. See Donald Ely (1990) and Donald Ely (1999); see also David Ensminger *et al.* (2004) and Barry Porter (2005).
9. See Carol Weiss (1993).
10. See Beth Gamse *et al.* (2002).
11. See Robert Godfrey (1973).
12. Gamse *et al.* (op cit) give the example of an educational intervention which intended to compare two methods of training school personnel: some were trained by university staff, while others were trained by utilizing a videotape series developed by the same university. The evaluators soon discovered that few schools had ordered the videotapes, and those that did, were not using them

appropriately. Hence that arm of the intervention had "disappeared."

13. See Gamse *et al.* (op cit), p. 156.
14. See Gamse *et al.* (op cit), p. 157.
15. As Annie Koh (2007) has put it, "you need to segment the people in the company by functions and give them what they need to get the job done."
16. See John Erich (2007).
17. See Gillis and Beauchemin, p. 60; also David Gallup *et al.* (op. cit.), p. 244 on "Refining."

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11

Training record-keeping

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Abstract: This chapter examines training record-keeping in the life sciences and other regulated industries. Record-keeping is necessary for any training system that is subject to audit. This necessity may come to be recognized as early as the point in program development when training assessments are created. It certainly comes to be recognized when the program is being implemented (or even piloted) and actual training records are generated. This documentation could include training records (or attendance sheets), training assessments, and curricula or individual training plans (ITPs). These documents could be in electronic form or hard copy. This chapter will first consider some strategic aspects of record-keeping, then turns to tactical issues.

Key words: accessible record, appropriately retained record, auditable record, authorized record, backed-up system, captured record, complete record, compliant organization, comprehensive record, consistent system, exportable record, identifiable record, implemented system, inviolate record, maintained record, Part 11 compliance, predicate rule, record-keeping audiences, responsible system, retrievable record, usable record.

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11.1 Introduction

In the mid-1990s, the University of Pittsburgh conducted a major study of functional requirements for record-keeping, called the Electronic Records Project.[1] Reporting on this project, and specifically describing records, Wendy Duff stated: "[Records] are created in the first instance to control or direct an organization and to help orient staff to a common goal or purpose."[2] That is, records serve the purpose of controlling and directing the organization. She continues:

> They have residual value because they document the outcomes of the directing and controlling activities and because they provide evidence of an organization's rights as well as its obligations to its staff and society. For records to fulfill these roles, they must be readable, understandable, and trustworthy.[3]

There are two main audiences for record-keeping: operational staff and various quality auditors. The operational perspective is typically proactive, while the auditor's perspective is typically retroactive. There are also other audiences, including the training unit itself.

Operational staff includes employees (the trainees) and their supervisors. Both employees and supervisors are interested in the trainees' currency in their individual training plans (ITPs), for purposes of work assignments. At the beginning of each shift, the supervisor wants to know if the employees on this shift are trained to the current versions of each and every standard operating procedure (SOP) that is listed in the ITP, that will be executed during that shift. The supervisor reviews the employees' training histories (i.e., the summary of the training records). Then the supervisor makes

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work assignments accordingly. Thus, the training records are used proactively to control and direct the organization.

Auditors include internal and external auditors (e.g., regulatory investigators, etc.) who are interested in whether the signer of the particular operational document (e.g., a batch record) was trained to the appropriate SOP before signing. The auditor reviews the signer's training history in light of a set of documents being inspected. In these cases, the training records provide evidence of the organization's past fulfillment of its regulatory obligations.

11.2 Record-keeping requirements

As the Electronic Records Project at the University of Pittsburgh has indicated, record-keeping requirements can be considered at several levels – that of the *organization*, that of the record-keeping *system*, and that of the *record* itself (Figure 11.1).

To begin with the highest level of requirements, the organization (i.e., Level I) must be *compliant* with all relevant legislation, regulations, and best practices concerning training records.[4]

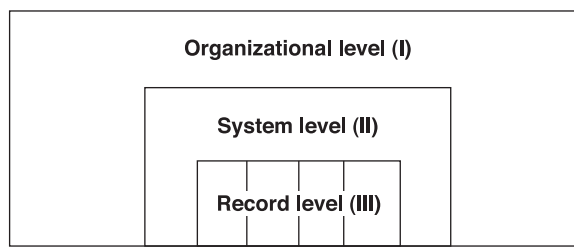

Figure 11.1 Levels of record-keeping requirements

At the second level of requirements, the training record-keeping system (Level II) – whether electronic, paper based, or hybrid – must be *implemented*, *responsible*, *consistent*, and *appropriately backed up* according to the following definitions:

- *Implemented* means that training events can be duly recorded in the system.
- A *responsible* system's controlled documents (i.e., SOPs for training record-keeping) are written and followed, plus the procedure clearly identifies the responsible party for each task.[5] As an example of the failure to meet this functional requirement, and its GXP implications, consider FDA Warning Letter to Arrow International, dated 10 October 2007: "According to procedure #CHR-001. 'Training Administration, Documentation, and Record-keeping Procedure,' your firm has 30 days to complete the training. One training requirement was over six months late."[6]
- *Consistent* systems have been validated, so identical processes generate identical outcomes. Vendors sometimes suggest that their software has been validated or audited. However, FDA has specifically stated that the organization using the software must validate it for that situation.[7]
- *Appropriately backed-up* systems protect documents from loss or corruption by being subject to a regularly scheduled backup. As an example of the failure to meet this functional requirement, see FDA Warning Letter to the Cordis Corporation in Warren, NJ, dated 1 April 2004: ". . . validation did not include testing and verification of back-up and restoration of the electronic data files."[8]

The documentation of the training itself can be viewed as a *captured record*, a *maintained record*, and a *usable record*.

The required characteristics of a *captured training record* are authorized, comprehensive, identifiable, and complete according to the following definitions:

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- *Authorized* training records have been created by an authorized person, for example a qualified trainer.
- *Comprehensive* means that a training record has been created for every training event. For an instance of not meeting this functional requirement, see FDA Warning Letter to Rhytec, Inc., dated 24 April 2007: "Documentation of training is not consistently maintained."[9]
- *Identifiable* means only one training record has been created for a given training event, and it is linked to that particular training event.
- *Complete* training records include all information about the training event, for instance, which employee was trained, on which SOP, by whom (the trainer), and at what time and date. As an instance of the failure to meet this functional requirement, consider FDA Warning Letter to Omnicare, Inc., dated 11 January 2007: "all of the employee records lacked the 'Supervisor Signature' to show that the training was given."[10]

Maintained records must be inviolate, auditable, and appropriately retained according to the following definitions:

- *Inviolate* is defined as any alteration or modification of the record is traceable, and further, that repudiation of the record is not possible. As an illustration of not meeting this functional requirement, consider FDA Warning Letter to Concord Laboratories, dated 11 July 2006: "Appropriate controls are not exercised over computers or related systems to assure that changes in analytical methods or other control records are instituted only by authorized personnel."[11]
- *Auditable* means that every use of the record leaves an audit trail. As an example of the failure to meet this requirement, see FDA Warning Letter to Concord

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Laboratories, dated 11 July 2006: ". . . review of audit trails is not required."[12]

- *Appropriately retained* training records must be subject to a retention schedule and then disposed according to procedure.[13]

*Usable training record*s must be exportable, retrievable, and accessible to authorized parties according to the following definitions:

- *Exportable* records must be portable from one system to another without loss of information.
- *Retrievable* training records are in a form that can be searched and retrieved within a reasonable period of time and expenditure of resources.
- Documents *accessible to authorized parties* must be available to those who are authorized to access them and unavailable to those who are not authorized.[14]

After identifying two main audiences for the documentation of training – operational staff and auditors – the training record-keeping must possess characteristics of good documentation management. If at each level – organization, training record-keeping system, and documentation of training – characteristics are present that are appropriate for that level and proceduralized, that level will be "audit proof," which is to say it can survive an internal or external GXP audit, and will moreover have business value to operational staff.

11.3 Part 11 compliance

When document management is discussed with reference to training and assessment, the topic of Part 11 compliance frequently comes up (Part 11 refers to "Electronic Records;

Electronic Signatures," which is Part 11 of 21 CFR). In keeping with the emergence of electronic technologies, FDA issued regulations in 1997 for e-records and e-signatures that sought to permit wide use of electronic technology, compatible with the protection of public health. Soon after they became effective, FDA announced a reconsideration of these regulations. In 2003, FDA withdrew the guidances that had accompanied the regulations. While the reconsideration of the regulations was under way, FDA indicated they would narrowly interpret the scope of Part 11 and promised to exercise enforcement discretion. During this period, records and record-keeping need still comply with the underlying regulations.

A typical example of FDA regulations and associated record-keeping is quality complaints about regulated products. 21 CFR 211.204 requires written procedures for the handling of all product quality complaints. This requirement ("predicate rule") further stipulates that "a written record of each complaint shall be maintained in a file designated for drug product complaints."

That is a second predicate rule; since it deals with record-keeping, it implicates Part 11, if the organization has chosen to manage that record electronically. Moreover, the initial regulation also stipulates that a record shall be maintained, should an investigation of the product complaint be conducted; or the record shall include the reason and the name of the person responsible for a decision not to conduct an investigation. That is a third predicate rule; since it also deals with maintaining records of investigations, it also implicates Part 11.[15]

Equipment cleaning and maintenance under good laboratory practice (GLP), good manufacturing practice (GMP), and medical device regulations have broader scope (Table 11.1). The cleaning and maintenance requirement

Table 11.1 Equipment cleaning and maintenance under GLP, GMP, and medical device regulations

Regulation	First Predicate Rule	Second Predicate Rule
21 CFR 58.63	(a) Equipment shall be adequately inspected, cleaned, and maintained	(c) Written records shall be maintained of all inspection, maintenance, testing, calibrating, and/or standardizing operations
21 CFR 211.67	(a) Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, integrity, strength, purity, and quality (SISPQ) of the drug product beyond the official or other established requirements	(b) Written procedures shall be established and followed for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product
21 CFR 211.182	Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, integrity, strength, purity, and quality (SISPQ) of the drug product beyond the official or other established requirements	A written record of major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments), and use shall be included in individual equipment logs that show the date, time, product, and lot number of each batch processed

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21 CFR 820.70	(g) Each manufacturer shall ensure that all equipment used in the manufacturing process meets specified requirements and is appropriately designed, constructed, placed, and installed to facilitate maintenance, adjustment, cleaning, and use	(1) Maintenance activities, including the date and individual(s) performing the maintenance activities, shall be documented

(first predicate rule) also stipulates that the cleaning and maintenance must be recorded (second predicate rule).[16]

The form of these typical regulations involves two aspects: a requirement (one predicate rule) that a task or activity be proceduralized and the SOP be followed, and a requirement (a second predicate rule) that an associated record be kept of the activity or task. The second predicate rule, dealing with record-keeping, implicates Part 11 if the organization had decided to manage the record electronically. Insofar as Part 11 is implicated, procedures and controls must ensure the authenticity and integrity of electronic records. Moreover, procedures and controls must hold individuals accountable and responsible for actions initiated under their signatures.

11.3.1 Training records

By contrast, the documentation of training, including training records and training assessments, is not covered by such predicate rules. FDA regulations for areas such as pharmaceutical and biopharmaceutical operations, clinical trials, medical device operations, or human tissue processors require that personnel be trained.[17] These are examples of the first predicate rule noted in Table 11.1.

The only requirement for documentation of training is found in FDA GLPs, where it is stipulated that "Each testing facility shall maintain a current summary of training and experience and job description for each individual engaged in or supervising the conduct of a nonclinical laboratory study."[18] That implicates a "current summary" of the individual's training records, which might take the form of the individual's training history, not the training records or training assessments themselves.

Regarding clinical trials, FDA stipulates that:

> A protocol is required to contain the following [. . .] The name and address and a statement of the qualifications (curriculum vitae or other statement of qualifications) of each investigator, and the name of each sub-investigator (e.g., research fellow, resident) working under the supervision of the investigator

on a given clinical study.[19] Notice that this predicate rule about "curriculum vitae or other statement of qualifications" of the clinical trials investigator was not extended to the subordinates, the research fellows, residents, etc.

Finally, the GMPs require "records shall be maintained stating the name, address, and qualifications of any consultants and the type of service they provide."[20] It is instructive that the rule-making that applied this predicate rule to the qualifications of consultants did not apply it to the majority of pharmaceutical operations employees and supervisors covered in 21 CFR 211.25.

FDA regulations are silent about training records for other areas such as pharmaceutical and biopharmaceutical operations, medical device operations, blood products processors, or human tissue processors.[21] Indeed, CFR Part 11 does not include such a requirement for itself. It requires

only a "determination that persons who develop, maintain, or use electronic record/electronic signature systems have the education, training, and experience to perform their assigned tasks," which is another example of the first predicate rule noted in Table 11.1.[22]

In light of this, the documentation of training does not fall within the scope of Part 11. What are the implications of this limited scope? We assume throughout that this documentation is controlled, as well as duly signed by the party responsible for the action described. The documentation of training can be considered as instances of what FDA has called a hybrid situation. In such a situation, paper record and signature components can co-exist with electronic record and signature components, "so long as [. . .] the content and meaning of those records are preserved."[23]

Consider the following scenario: A GXP training event – either technical training or regulatory training – has just occurred. All the trainees have been assessed as "successful" in the training. There is a training record – a controlled document – and its use is proceduralized, including entry into a validated Learning Management System (LMS). Trainees then sign and date the paper-training record, and the trainer countersigns and dates the record. At this point, the event is fully documented; the trainees are fully trained to perform the GXP tasks. They can "touch" the product or supervise those touching the product. Then, according to procedure, duly authorized data entry clerks enter the data from the training record into the LMS within 72 hours, and sign off the entries. A duly authorized data steward verifies the data entries and signs off. At this point, by procedure, the electronic record becomes the controlled document, and the paper copy can be archived or disposed of.

Sounds straightforward; however, there have been situations where it is assumed that all training records fall

within the scope of Part 11. Instead of the scenario outlined in the previous paragraph, the documentation of the training event is treated like a regulatory submission, say, where each of the parties involved must provide an electronic signature to the electronic record. So the "draft" training record is routed to each trainee for their review and electronic signature, then is routed back to the trainer for review and electronic signature, and finally routed to quality assurance (QA) for "release." The number of "transactions" increases dramatically. When finally released, the training record ceases to be a draft, and becomes "effective." Before the training record became "effective," employees who had just been trained were instructed not to "touch" the regulated product.

In a study of a random sample of training records (n = 11) processed this way, involving employees – not consultants, non-clinical lab staff, nor clinical trials investigators – the average time between the conclusion of the training event and the "release date" was 10 days.

If training records had been recognized as outside the scope of Part 11 and the first scenario had been followed, the time between conclusion of the training event and the full documentation of the training would have been about 10 minutes – the time it takes the trainer to check all the trainees' signatures and dates and countersign the training record.

FDA regulations require that personnel touching the product be trained. The regulations, with few exceptions, do not address training records, including training assessments. It is important to review carefully the cases where the regulations do apply and ensure compliance. It is equally important to ensure that the organization is not wasting time and resources in overbuilding (i.e., hyper-scoping the training record-keeping process).[24]

11.4 Tactics of training record-keeping

Training record-keeping includes training records (or attendance sheets), training assessments, and curricula or ITPs. In each case, this is a controlled document; each has necessary fields and optional ("nice-to-have") fields. An example of a "nice-to-have" feature of a training record would be a field where a supervisor vouches for the record creator's qualification.

Training records, for instance, have a number of necessary fields. These fields are listed in Table 11.2, insofar as the documentation corresponds to the first scenario.

The training procedure must not only list each of these fields, plus any optional "nice-to-have" fields, but must indicate the roles and responsible party for each field. If the training SOP describes a fully electronic scenario where trainees record their participation in the training event online, and trainers also record their facilitation of the event online, the SOP must also describe the fall back process in the event there are connectivity problems, training in remote locations, etc. Thus the roles and responsibilities of the data clerk and data steward are still critical.

If hard copies are archived following data entry into the validated LMS, they should be placed in the document repository with, at a minimum, the following indexing information: record type, file names, date ranges, and positions (titles of personnel), who are authorized to access the archived records. Or, by procedure, the hard copies should be appropriately disposed.

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Table 11.2 Necessary fields in training records

	Field	Comment
1.	Employee (Trainee) Name	This name must correspond to the employee's name as entered in the annually renewed signature card
2.	Employee ID Number	Temporary employees, etc. who do not have an authenticated network login must be provided with a unique ID number
3.	Course/SOP Name	What is the organization's naming convention?
4.	Course/SOP Number	What is the organization's numbering convention?
5.	Type of Training	This includes one of a number of delivery modalities – classroom, e-learning, coaching, etc.
6.	Date of Training Event	What is the organization's date/time convention?
7.	Trainer's Name	This name must correspond to the trainer's employee name as entered in the annually renewed signature card
8.	Trainer's Employee ID Number	Consultants, etc. who do not have an authenticated network login must be provided with a unique ID number
9.	Data Clerk Name	[See comment to # 1 above]
10.	Data Clerk's Employee ID Number	[See comment to # 2 above]
11.	Date Entered into LMS	[See comment to # 6 above]
12.	Data Steward Name	[See comment to # 1 above]
13.	Data Steward's Employee ID Number	[See comment to # 2 above]
14.	Date Verified	[See comment to # 6 above]

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11.5 The training unit as audience

The training unit itself is another audience for the documentation of training. First, the training unit can use training records to document the level of effort of the unit. This documentation can be used in annual budget sessions to justify requests for more training staff or other resources.

Second, the training unit can use training records and training assessments to test the accuracy of statements about training.

Documentation of training impact can be represented as a continuum ranging from an endpoint reflecting training inputs to an endpoint reflecting training outputs (Figure 11.2).

At the first endpoint on the continuum, training impact is documented by staffing levels of the training unit. The supposition is, "The larger the training staff, the greater the training impact." This is clearly only a measure of inputs, a very rough proxy for training impact.

At the other end of the continuum, training impact is documented by return on investment (ROI) for training. This can be calculated in a number of ways. For instance, the marginal benefit/cost ratio is the change in trainee proficiency divided by the change in the training unit's expenditure on this training module.[25] ROI is clearly a direct and salient measure of training outputs. Effective training leads to improved performance, hence performance measures should

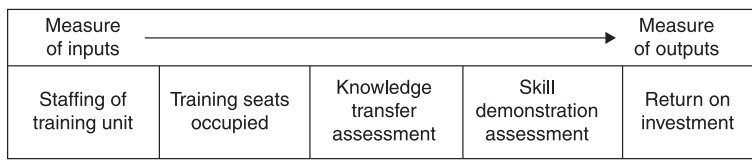

Figure 11.2 Continuum of training impact

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be used to document training impact. These measures might include numbers of documents with defects, amount of rework, and other business metrics.

The number of seats occupied in training sessions falls on that continuum, somewhere between staffing levels and ROI, nearer to the rudimentary endpoint of staffing levels.[26] Other points on this continuum of the documentation of training impact include training assessments such as knowledge transfer assessments (KTAs) and skill demonstration assessments (SDAs).[27]

How can training documentation be used to test the accuracy of theoretical statements about training? Consider the following statements and accompanying graphic by Harold Stolovitch: "Because training is costly and removes workers from productive tasks, we expect significantly improved performance after training. Reality, however, is usually very different, as illustrated by the post-training solid line" (Figure 11.3).[28] These statements and the graphic are quite intriguing to trainers.

Two methodological questions about Stolovitch's figure arise: What kind of evidence would be required to determine

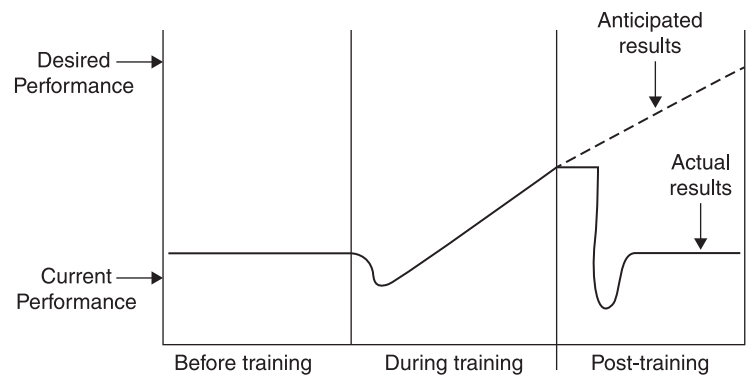

Figure 11.3 Post-training performance

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whether there is a dip in performance during the training event (the second panel in the triptych)? What kind of evidence would be required to determine if there is a dip in performance following training (the third panel in the triptych)?

This chapter stresses the methodological point that the answer to each question depends on continuous tracking of performance – throughout the training event for the first question, and during the immediate post-training period for the second. Such tracking, taking the form of performance assessments (most likely in the form of SDAs), will require a substantial record-keeping effort.

In the typical case, however, assessments are conducted at only two points in time – one a pre-training assessment just before the training event, and a second, post-training assessment, say an "intermediate test" conducted after the trainees have returned to the job. Given only two data points, the average performance level would appear to be a straight line, perhaps upward-sloping to the right, perhaps flat; in any case we would not be able to address the questions about Stolovitch's figure.[29]

These uses of the documentation of training do not have the enterprise-wide significance of the other two audiences – the operational use and the auditor's use. The operational staff represents the line of business. This audience and its proactive use of training records for work assignments directly relate to the bottom line. The auditors represent the regulatory requirements within which the organization will be profitable (or not).

The training unit is usually viewed as an overhead department, engaging in capacity building and thereby (only indirectly) contributing to the bottom line. Donald Kirkpatrick and others have held that "trainers must justify their existence."[30] An effective training department should

address business performance issues, and "justify their existence" by pointing to the improved performance of the workforce. Otherwise the training department will be viewed as overhead and not active contributors. In this sense, trainers are indeed an audience for training record-keeping. However, we see that this is a distinctly secondary audience, behind the two major audiences.

Good training record-keeping may well contribute to a corporate climate that supports widespread and disciplined use of organizational metrics. Such metrics allow benchmarking and trending to enhance organizational control.

11.6 Conclusion

There are two main audiences for training records, operational staff and auditors. In addition, there are other audiences such as the training unit itself. To serve these audiences, training record-keeping must possess characteristics of good document management. At each level of the organization, document management must be appropriate so that training record-keeping will be "audit proof," and will, moreover, have business value to operational staff.

Regulatory compliance, as it relates to training record-keeping, requires that personnel touching the product be trained. FDA regulations, with few exceptions, do not address training records. It is important to review carefully the several cases where the regulations do apply and ensure compliance. It is equally important to ensure that the organization is not wasting time and resources overbuilding the training record-keeping process.

The fields that are necessary for training records, as well as necessary roles and responsibilities, need to describe the fall-back process in case there are access or other system problems

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in a fully electronic approach to training record-keeping. Validated electronic training tracking systems should be employed to manage training records and training assessments in an effective manner.

Training records can provide data to justify budget requests. They can provide data to test the accuracy of statements about training. The training unit's use of these records will not have enterprise-wide significance; yet, such use can contribute to the overall impact of organizational metrics.

11.7 Notes

1. See Margaret Hedstrom (1993) and David Bearman (1994).
2. See Wendy Duff (1995), esp. p. 29.
3. See Duff, op. cit., p. 29
4. See Duff, op. cit., pp. 33–5. These are functional requirements of record-keeping, not necessarily GXP regulatory requirements. As we shall see, the functional requirements do have GXP implications. For the current situation on organizational compliance, see Roger Matus (2007) and Darwin Stephenson (2007).
5. See Chapter 5.
6. Available at *www.fda.gov/foi/warning_letters/s6537c.htm*. See also "Arrow warned about quality systems," *Reading Eagle*, 16 October 2007.
7. *Federal Register*, Vol. 62, No. 54 (20 March 1997), "Rules and Regulations," p. 13445. See also Gwendolyn M. Wise-Blackman (2006): "validation must be achievable with staff at the work site."
8. Available at *www.fda.gov/foi/warning_letters/archive/g4601d.htm* See also "Federal Regulators Find Fault

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with Stent-Making Practices at Florida's Cordis," *Miami Herald*, 6 April 2004.

9. Available from: *www.fda.gov/foi/warning_letters/s6341c.htm*
10. Available from: *www.fda.gov/foi/warning_letters/g6208d.htm*
11. Available from: *www.fda.gov/foi/warning_letters/archive/g5973d.htm*
12. Available from: *www.fda.gov/foi/warning_letters/archive/g5973d.htm*
13. See Laurie Fischer (2006); also Ellie Myler (2006) and Tina Torres (2006).
14. Authorization involves authenticated users; usually this is two-factor authentication involving two of the threefactors: (a) What you know (e.g., a password), (b) What you have (e.g., a security swipe card), and (c) What you are (e.g., a biometric characteristic). See Joan Engebretson (2006); Bruce Schneier (2005).
15. On predicate rules, see Tammala Woodrum (2003). See 21 CFR 211.198 (a) on the requirement of written SOPs, 211.198 (b) on the requirement of written records for each complaint, and 211.198 (b) (2) and (3) on the requirement of written records for each investigation or the decision not to investigate.
16. For GLPs, see 21 CFR 58.63, "Maintenance and calibration of equipment;" for GMPs, see 21 CFR 211.67, "Equipment cleaning and maintenance;" also 21 CFR 211.182, "Equipment cleaning and use log;" and for medical devices, see 21 CFR 820.70, "Production and process controls."
17. For pharmaceutical employees, see 21 CFR 211.25; for biopharm personnel, 21 CFR 600.10; for non-clinical lab personnel, 21 CFR 58.29; for medical

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device personnel, 21 CFR 820.25; for human tissue recovery personnel, 21 CFR 1271.170.

18. See 21 CFR 58.29 (b), "Personnel." As Robert McDowell (2004) has put it "It appears that Part 11 would not apply to computerized systems holding GMP training records, in contrast to GLP systems holding similar records where the rules would apply."
19. See 21 CFR 312.23(a)(6)(iii)(b). A curriculum vitae is more a record of educational attainment than a training history. Since the protocol is part of the IND regulatory submission, it will implicate Part 11 on that ground.
20. See 21 CFR 211.34, "Consultants."
21. But see Wise-Blackman, op. cit., p. S-10, who repeatedly refers to "software that is 21 CFR Part 11 compliant and houses a database of training records." The software that she advocates is not justified in terms of predicate rules – as we have seen, there are not any – but as follows: "One benefit of compliant training software is the ease of routine scheduling of required training" and "Routine retraining can be accomplished efficiently through the use of group sessions or individual web-based compliant software." Of course, "routine scheduling" and "routine retraining" can be more easily and efficiently accomplished with any validated training tracking system, regardless of its Part 11 compliance.
22. See 21 CFR 11.10 (i); see however Office of the Commissioner, "Guidance for Industry: Computerized Systems Used in Clinical Investigations," Washington, DC: FDA (May 2007), p. 7:

> Those who use computerized systems must determine that individuals (e.g., employees, contractors) who develop, maintain, or use computerized systems have the education, training, and experience

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> necessary to perform their assigned tasks . . . We recommend that computer education, training, and experience be documented.

Neither a guidance nor a recommendation constitutes a predicate rule.

23. Office of Compliance, CDER, "Guidance for Industry; Part 11, Electronic Records; Electronic Signatures – Scope and Application," Washington, DC: FDA (August 2003), note 8. On the choice between electronic, paper-based, and hybrid record-keeping systems, see Rakesh Shukla (2004). See also Dan Riordan (2007), who echoes the first predicate rules on page 33:

> The FDA requires that medical device manufacturers and pharmaceutical companies give their employees adequate training in their job responsibilities, and in their roles in ensuring the quality of a company's goods and services.

Riordan continues with a list of software functions:

> In compliance software systems, users can create documentation for training requirements, job descriptions, qualification definitions, courses, work instructions, and many other criteria. System administrators can configure multiple levels of secure access, so that all employee records remain confidential. Many systems have capabilities for managing and tracking employee certifications, scheduling courses and training sessions, and monitoring employee performance. Approved changes to documentation can automatically update employee training records and simultaneously notify appropriate employees and

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managers of the need for retraining on these documents. Automating these processes makes it much easier to keep employee records updated, and is an important element in FDA compliance.

24. See Tammala Woodrum, op. cit., esp. pp. 162–3 on the problem of organizational "policies that potentially expand the scope of Part 11." FDA has indicated that Part 11 was never intended to "significantly increase the costs of compliance to an extent that was not contemplated at the time the rule was drafted," nor was it intended to "discourage innovation and technological advances without providing a significant public health benefit." See Office of Compliance, CDER, op. cit. A hybrid record-keeping system might best address the situation where the vast majority of training documents would be maintained in electronic form, and the few exceptions would be managed in paper form.
25. See Jack Phillips and P. Phillips (2007) and Jack Phillips (2007), esp. p. 18.
26. Chris Moore (2007) refers to the number of seats occupied in training sessions as "fill rates."
27. It is not the case, contrary to Wise-Blackman, op. cit., p. S-10, that "documenting the transfer of knowledge about the SOP is best accomplished through a web-based system that incorporates short quizzes as a prerequisite to receiving approval for training," because there is a substantial legal exposure to the use of unvalidated KTAs (short quizzes), and there are serious costs to validating KTAs. The trainee's completion of prerequisites would best be ascertained through a SDA, as would the documentation of trainee proficiency.
28. The quotation and figure are from Harold D. Stolovitch (2007).

29. Charles Tennant, M. Boonkrong, and P. Roberts (2002) have suggested three kinds of post-training assessments – an "immediate test" when the training has been completed, an "intermediate test" when the trainee has returned to the job, and an "ultimate test" to measure behavioral changes.
30. See Donald L. Kirkpatrick (1994). The best justification for trainers' existence is probably record-keeping that satisfies the needs of operational staff and GXP auditors.

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12

Formative evaluation

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Abstract: This chapter will consider the possibilities for formative evaluation of training programs as well as any other kind of program, within the framework of the program improvement model. Specifically, the question is whether the formative evaluation of training programs can utilize the full range of experimental and quasi-experimental designs, as well as any other approaches. The possibilities of employing adaptive designs will be considered. Thereby, the data gathered in that evaluative effort can at the same time be made available to management, during the course of the training process, to allow decisions to be made about program improvement. FDA has recently expressed interest in the use of adaptive designs in clinical trials.

Key words: adaptive design, continuous feedback of evaluative findings, final implementation, formative evaluation, pilot implementation, program improvement model, randomized clinical trial (RCT), summative evaluation.

12.1 Introduction

Program evaluation depends upon program implementation. If a program has not ever been implemented, then there is nothing to evaluate – nothing except the absence of implementation itself.

As we saw in Chapter 9, there are two kinds of implementation – Pilot Implementation and Final Implementation. In the case of a pilot implementation, the results of the program evaluation can be fed back, closing the loop, facilitating further refinement of the training program. This is called a "formative evaluation." As Robert Gagné and Leslie Briggs have stated, "Formative evaluations provide data on the basis of which to revise and improve the materials, the lesson plans, the performance tests, and indeed the operation of the entire instructional system."[1] If the evaluation shows that the training module has shortcomings, those shortcomings are fed back to be analyzed again. Further design and development efforts follow, until the module meets organizational needs. Thereupon there is a final implementation, and an evaluation that documents the extent to which the training program meets the organization's needs. This is called a "summative evaluation." Gagné and Briggs state:

> Summative evaluation is usually undertaken when development of an instructional entity is in some sense completed, rather than on-going. Its purpose is to permit conclusions to be drawn about how well the instruction has worked.[2]

The program improvement model can be conceptualized as having two paths leading out of the development phase. One path leads to pilot implementation, followed by

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formative evaluation, from which a feedback loop allows further analysis, design, and development. At some point, determined by management, the training program is judged to be ready for the other path. As Gagné and Briggs[3] have pointed out:

> There is no standard number of formative evaluations that small components or segments or the entire system undergo. The number depends on the budgets and time available, the degree of excellence set as the system design objective, and the total circumstances surrounding the project.

The program then moves to final implementation, followed by summative evaluation (Figure 5.2).

There are several ways to conceptualize the program improvement model at this point. One is to include pilot implementation and formative evaluation within the development phase. When the pilot and the formative evaluation are completed, the program moves into the (final) implementation phase, followed by the (summative) evaluation phase. Another conceptualization is to include two types of implementation, pilot and final, within the implementation phase, and two types of evaluation, formative and summative, within the evaluation phase. These different conceptualizations bear on the logic of the program improvement model, but not on the process of program development.

As a final introductory point, it is clear that management has one very significant role in a formative evaluation; that is specifying the overall goal, and level of effort, for the evaluation. What might be management's response to evaluative findings gathered during the formative evaluation of a program? The response of the program designers and

developers to evaluative findings is clear; they will consider making program improvements based on the evaluative findings. What about the response of management?

12.2 Feedback versus research design

The question often arises in the formative evaluation of a training program or other program: what is the effect of the dissemination of evaluative findings during the life of the program? It is often assumed that the "experimental design" dictates that intervention (e.g., training materials, training "script," etc.) must remain invariant during the program cycle. Friedman, Furberg, and DeMets[4] state that a clinical trial study protocol:

> should be developed before the beginning of subject enrollment and should remain essentially unchanged except perhaps for minor updates. Careful thought and justification should go into any changes. Major revisions which alter the direction of the trial should be rare.

If preliminary findings were fed back, this would allow a modification of the training materials and other aspects of the program, thus invalidating design and the evaluative research findings.

This position has until recently been held regarding clinical trials in the pharmaceutical industry. As Derek Lowe[5] has expressed it, in a clinical trial:

> establish your "null hypothesis" (typically that your drug is no better than a placebo or the current standard

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> of care) and you start collecting data, in the hopes that you will fail to prove it. Everything stays carefully blinded. The investigators have no idea what they are administering and the patients have no idea what they're taking until a predetermined endpoint – to do otherwise would destroy the statistics.

Notice the significance of "blinding" in clinical trials, particularly "double blinding," where both subjects and investigators are unaware of the assigned intervention – whereby findings for program improvement cannot straightforwardly be fed back.[6] In contrast to the logic of blinding, the actual conduct of blinding in randomized clinical trials (RCTs) has been assessed in several recent studies, including Boutron *et al.*[7] and Fergusson *et al.*[8]

This position has been held by researchers outside the field of clinical trials as well: Michael Brooks[9] states that continuous feedback of evaluative findings ". . . has the unfortunate effect of tossing a monkey-wrench into the research design constructed at the program's outset." Daniel Stufflebeam, a leading figure in the program evaluation community, describes the development of his own position:

> I had to reject basically everything I had thought necessary for evaluating educational projects, including behavioral objectives, experimental designs, and standardized tests. Instead, I advised educators to key evaluations to provide information for decision-making.[10]

The argument against the "experimental method" is a methodological, not a practical argument.[11] The critics of

experimental design are speaking of characteristics inherent to evaluation theory that account for a sharply limited utility. The critics are not suggesting that formative evaluation would be more successful if the experimental designs were more precisely constructed, if randomization of subjects were more diligently pursued, or if experimental methods were more carefully practiced. According to the critics, experimental method in program evaluation, especially RCT, is inappropriate if not defective.

The importance of this matter can hardly be overstressed. As indicated above, feedback of evaluative findings is of vital importance for improving the process in training and development. If there is an incompatibility between feedback and the "experimental method," one obviously must be abandoned. But to abandon the former, evaluators forego their mandate to provide timely and relevant information for program adaptation. To abandon the latter, they seriously limit the research techniques they have available for evaluating the program; instead of Donald Campbell and Julian Stanley's famous *Experimental and Quasi-experimental Designs*, the formative evaluator is restricted to just the quasi-experimental designs and even more inferior approaches, such as "pre-experimental designs."[12] As Green states, "RCTs are the gold standard of treatment trial methodology, and to deprive complex (often psychosocial) interventions of their imprimatur is potentially to undervalue these areas in an evidence-based climate."[13] Moreover, this limitation sacrifices what rigor the evaluators' discipline has. However, we find that the critics of "experimental design" have misplaced their criticism.

The next section will give an existence proof that formative evaluation can be conducted within the framework of experimental design, and evaluative findings can at the same time be provided for improvement of the training

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program. This means that the full range of evaluative approaches is available to the formative evaluator, including experimental designs (i.e., RCT) as well as quasi-experimental designs.

12.3 The good news, part 1

It is not the case that training intervention must remain invariant. Program enhancement, in light of feedback from a formative evaluation, can take place concurrently with an evaluation in the framework of the RCT experimental design. Of course, desirable modification practice does not (or should not) mean a hodgepodge array of "random" interventions resulting from poor program definition; this should have been pre-empted in the design phase of the program improvement model. Nor should "random" interventions result from the capacity of those who implement training programs to understand adequate definitions; that should have been addressed in the implementation phase.[14] It makes no difference, for the experimental method, whether an evaluative judgment of program ineffectiveness is available for program adaptation or not. It makes no difference, for the experimental method, whether changes in training intervention are implemented or not. Evaluators can fill their mandate for dissemination of timely data and concomitant programmatic change.

The evaluator can realize, based on an on-going program evaluation, that "training intervention G will not produce the desired results." The intervention can be revised in the "middle of the stream," so to speak, and evaluators can still complete their formative evaluation.

The dissemination of evaluative findings through an appropriate study monitoring committee, and a managerial

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reaction to such findings, enhancing the likelihood of program success, will not invalidate the evaluation effort, even though an initial judgment predicted program failure. Only a misunderstanding of the nature of evaluative research could foster the view that the training intervention is fixed.

Assume that an evaluation of a training program is underway. The program, in essence, takes a set of inputs and given conditions, Z, and by means of some process, G, transforms the inputs into an output described by the dependent variable, x. We assume x to be a behavior. The dependent variable may be a business measure, such as number of reworked batches, or an index, such as Occupational Safety and Health Administration (OSHA) recordables. The evaluator is randomly assigning employees to control or treatment groups, manipulating variables, recording and communicating results, etc.

Thus behavior x is a function G of a complex state of affairs z, given by:

$$x = G(z) \qquad [12.1]$$

This says G and an index z of the set of independent variables Z are sufficient for the prediction of the dependent variable x, in the absence of dissemination of G or z. This can be represented by a two-dimensional diagram (Figure 12.1).

We note that for a given interval [z(o), z(i)], x will have a range of [x(o), x(i)]. Thus z might be an index of prior training history, on-the-job experience, etc. and x, a measure of productivity such as unit output, impounded batches, or quantity reworked. The set Z would include such items as appear in the employee's training history, etc. We assume throughout that the interval of x is continuous and closed.

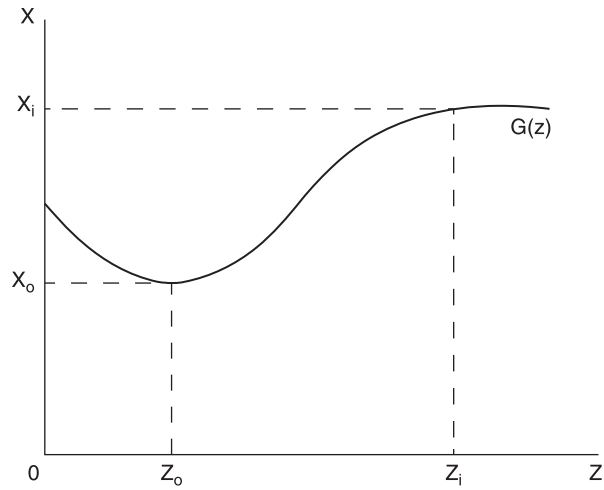

Figure 12.1 Performance levels of hypothetical program

12.4 The coexistence of RCT and dissemination of results

Consider the following scenario. G is the training and qualifying process, exemplified in a particular training program and including training materials, training "scripts," etc. Through an appropriate channel such as the study monitoring committee, the program manager has discovered a credible RCT evaluation report indicating that some aspect of G was tending to increase the quantity of rework. Suppose this aspect was the hour in the shift (i.e., whether the training event occurs early in the shift or late). Suppose further that the manager would be held accountable for the increase of rework. Then the manager might react to the report and implement a programmatic change from G to G*. An example of such a change would be mandating that all training programs be offered early in a shift. Then the output, rather than being x would be x*.[15]

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Let a reaction function R be introduced, indicating the dependence of the actual outcome x^* on the program manager's knowledge of the disseminated judgment (or prediction) of x. This is given by:

$$x^* = R(x) \qquad [12.2]$$

Given the relevant range [x(o), x(i)] we can represent the reaction function by a two-dimensional diagram (Figure 12.2).

With the variance of x through the range x(o) to x(i) will be associated a variance of x* between x(o)* and x(i)*. If R(x) is continuous over [x(o), x(i)], and if R(x) is bounded (i.e., 0 < R(x) < F) then by the generalized Brouwer Fixed-point Theorem there exists at least one x and one x* such that, x = x*. Also, for x = x*, the system described by Eqns 1 and 2 is in equilibrium (i.e., the manager will cease to react to x).[16]

Thus, for x = x*, that value of x is the correct public prediction, as well as the correct formative evaluative judgment.

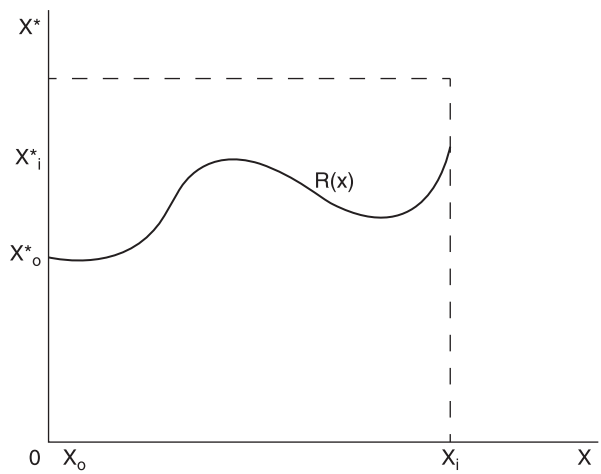

Figure 12.2 Reaction function for hypothetical program

In this section, we have shown that formative evaluation can be conducted within the framework of experimental design, and evaluative findings can at the same time be provided to the manager of the training program that is being evaluated, via the study monitoring committee or another appropriate channel. This means that the full range of evaluative approaches is available to the formative evaluator, including not only quasi-experimental designs but experimental designs (i.e., RCT) as well.

12.5 The good news, part 2

The preceding material incorporated an existence proof, showing that under specified conditions, training program modification could take place in response to evaluative findings developed within an experimental design. The following questions can still be raised: What are the implications of this for evaluation practice? Does anyone care? The answer to these questions is yes.

Let us look at a methodologically analogous situation, that of clinical trials of investigational new drugs. There is a long history of interest in adaptive designs in clinical trials, dating from Abraham Wald's pioneering research in the 1940s.[17] The FDA has expressed interest in adaptive clinical trials and the associated research designs. The dilemma of clinical trials has been described well by Lowe:

> In too many cases, the chief result of a trial is to show that the trial itself was set up wrong, in ways that only became clear after the data were unblinded. Did the numbers show that your dosage was suboptimal partway into a two-year trial? Too bad – you probably weren't allowed to know that. Were several arms of

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> your study obviously pointless from the start? Even if you knew, what could you do about it without harming the validity of the whole effort?[18]

The problem is to conduct clinical trials so that both the rigor of the experimental design (RCT) will be maintained throughout, and program revision can occur, based on the timeliest data. And, methodologically speaking, that is precisely the problem cited by Lowe, with reference to the evaluation of training programs.

As Scott Gottlieb, FDA Deputy Commissioner for Medical and Scientific Affairs, has expressed it, FDA is interested in "adaptive sampling designs, including response-adaptive designs for statistical experiments, where the accruing data from experiments – the observations – are used to adjust the experiment as it is being run."[19] He goes on to say:

> . . . the advantages of these approaches, rigorously designed, are becoming more evident, including among the ranks of our experts at FDA. It is essential that we at the FDA do all we can to facilitate their appropriate use in modern drug development.

Gottlieb discusses several adaptive approaches to the design of experiments, including the following:

- In an adaptive clinical trial, patient outcomes can be used as they become available to adjust the allocation of future patients or some other aspect of the study design.
- A second type of adaptive trial design involves on-going assessment of the sample size, to avoid under- or over-allotment of patients.[20]
- [Another includes] seamless designs that allow learning to be more iterative and less method-limited. That allow

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> continuous discovery that is not defined by phases but rather by what we learn as we go.[21]

Gottlieb acknowledges that:

> . . . adaptive approaches are not a panacea to all of our challenges, and enabling them is not a sure thing. Adaptive procedures are more complicated to design and to analyze, and in some settings are more difficult to implement.

Moreover, he is well aware of:

> . . . trepidation about the use of adaptive features and reluctance to consider a variety of enrichment and adaptive designs. In many cases, researchers are still unaware of the option to use adaptive designs because standard statistical courses and packages do not include them.[22]

There are political and ethical issues here as well. Steve Zisson notes:

> Purists will argue that changing a trial midway through a study somehow benefits pharmaceutical companies by potentially allowing them to manipulate results. Some worry that bias is more likely when results are known during the trial, compared with keeping trials blind.[23]

Concrete proposals are under consideration to mitigate such worries.[24]

Since FDA is interested in adaptive designs for the study of investigational new drugs, it is unlikely they would object to the use of adaptive designs in the formative evaluation of

training programs. What is methodologically appropriate for clinical trials can just as well work for the evaluation of training initiatives.

Several uses of such adaptive designs include the following:

- The formative evaluator can communicate interim training outcomes through a channel such as the study monitoring committee to the program manager, allowing timely revision of the training intervention, including revision based on comparison of programmatic alternatives.
- The evaluator can use interim training outcomes to allow more effective assignment of trainees to particular training sessions, for example by sequential sampling.

Gagné and Briggs maintain that "The manner of conducting formative evaluations varies widely".[25]

We are suggesting that one approach to formative evaluation of training programs is utilizing an adaptive RCT design. Gagné and Briggs maintain that "Quantitative data are definitely necessary for formative evaluation".[26]

The steps in conducting a formative evaluation can be summarized as follows:

1. The first step is to develop a formative evaluation plan for the training module, including an evaluation design, and any evaluative instruments.
2. The second step is to collect evaluative data as you begin to pilot the training module, including data from both the pilot trainees and from your training and development peers.
3. The third step is to review all the evaluative data you have gathered, in light of the statistical portion of the formative evaluation plan.

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4. Then, prepare an evaluation report summarizing the evaluations; propose revisions to the training module.
5. Get the study monitoring committee as well as management approval of these revisions.
6. The sixth step is to utilize the feedback for program improvement.
7. Then, continue the pilot (with further adaptations as required), until management is satisfied that the training module meets the organization's needs.

The essence of this process is the negotiation between the evaluator and program manager. This negotiation works toward a settlement that takes into account both methodological rigor on the one hand, and program goals and values on the other.

12.6 Management's prerogative

Management has an overarching role in a formative evaluation. That role is to specify the overall goal, and level of effort, for the evaluation. What does management want from this evaluation? There is a range of possibilities here. Does management want the most credible evaluative report possible? Or does management want the most blatant problems in the pilot project to be corrected? The evaluator must negotiate with management to determine the actual goal.

Once management's goal is set, the evaluator can recommend approaches to aspects of the formative evaluative design, such as the following:

- parallel group or cross-over design;
- recruitment of trainees;
- random assignment;

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- blinding;
- sample sizes;
- statistical analyses.

With recommendations of costs and benefits of each approach, management can decide between the approaches. A memorandum of understanding between management and evaluator can then be prepared, including a statement of the level of effort that will be required to attain the goal that management has set.

At that point the evaluator can begin to plan the logistics of the formative evaluation. The primary audience for this evaluation will be the instructional designer who will make program revisions as warranted.

12.7 Conclusion

This chapter has reviewed the possibilities for formative evaluation of training programs as well as any other kind of program, within the framework of the program improvement model. It can be concluded that the formative evaluation of training programs can utilize the full range of experimental and quasi-experimental designs, as well as any other approaches. In this chapter, the possibilities of employing adaptive designs have been considered. Thereby, the data gathered in that evaluative effort can at the same time be made available to management, during the course of the training process, to allow decisions to be made about program improvement. FDA has recently expressed interest in the use of adaptive designs in clinical trials.

This does not mean that the evaluator must use any particular design or approach. While the full range of methods and techniques are available, the decision about which of those

techniques and methods to use will depend upon two factors. One is management's goal for the evaluation; the other is the needs of the main audience of the formative evaluation, namely the needs of the instructional designer who will revise the training program. The formative evaluation and re-piloting of the training module can continue until management has decided that the needs of the organization have been met. Once the formative evaluation has been completed and all necessary changes to the module have been made, it is time to move to final implementation of the training program.

12.8 Notes

1. See Robert Gagné and Leslie Briggs (1979) p. 37 see also p. 290:

   > Evidence of an instructional program's worth is sought for use in making decisions about how to revise the program while it is being developed. In other words, the evidence collected and interpreted during the phase of development is used to form the instructional program itself.

2. See Gagné and Briggs, op. cit., p. 293. See also Joseph S. Wholey (1996)pp. 145ff and Greg Wang and Diane Wilcox (2006), esp. pp. 529–30.
3. See Gagné and Briggs, op. cit., p. 38.
4. See Lawrence Friedman, *et al.* (1981).
5. See Derek Lowe (2006), esp. p. 72.
6. See, for example, Kathryn Webert (2007); also Damian McEntegart *et al.* (2007). A classic statement is found in Friedman *et al.* op. cit., pp. 58–67.
7. See Isabelle Boutron *et al.* (2006).
8. See Dean Fergusson et al. (2004).

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9. See Michael P. Brooks (1965); see also Susan Jacobson *et al.* (2006), esp. p. 1518: "Adherence to an experimental design [. . .] may preclude some of the flexibility managers have experienced previously."
10. See Daniel S. Stufflebeam (2003). See also Stufflebeam (1967):

> . . . the application of experimental design to evaluation problems conflicts with the principle that evaluation should facilitate the continual improvement of a program. Experimental design prevents rather than promotes changes in the treatment because treatments cannot be altered in process if the data about differences between treatments are to be unequivocal.

Subsequently, in Stufflebeam (1975) he maintained that "experimental design often would not provide timely feedback for decision making." See also Stufflebeam (2001):

> . . . almost everything I had learned about experimental design, measurement, and statistics was largely irrelevant to evaluating new, heavily funded, but ill-defined projects [. . .] Gradually, I began to evolve an approach to evaluation that seemed to work [. . .] The approach was directed to designing evaluations that would address stakeholders' evaluative questions and provide them a flow of timely, relevant information.

11. On the often misused term methodology, cf. Fritz Machlup (1963).
12. See Donald T. Campbell and Julian C. Stanley (1963).
13. See Jonathan Green (2006).

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14. As Gallo *et al.* (2006) have put it regarding desirable modification practice, "changes are made 'by design,' and not on an *ad hoc* basis; therefore, adaptation is a design feature aimed to enhance the trial, not a remedy for inadequate planning;" esp. p. 276. On the project management requirements this raises for the roll-out and maintenance of a training program, see John N. Fabac (2006).
15. See Gordon Welty and Alfred Beradino (1971). The general treatment of these cases is given in Emile Grunberg (1967). Cf. also E. Grunberg and Franco Modigliani (1954).
16. See Andrzej Granas and James Dugundji (2003).
17. See Abraham Wald (1950); also Wald (1947) and Oskar Morgenstern (1951). See also Friedman *et al.*, op. cit., pp. 48–52 and pp. 144–54.
18. See Derek Lowe (2006) op. cit., p. 72.
19. See Scott Gottlieb (2006). See also Anna W. Mathews (2006).
20. See also Paul Gallo, op. cit., pp. 281–282.
21. See also Paul Gallo, op. cit., pp. 280–281.
22. See Scott Gottleib, op cit.
23. See Steve Zisson (2006).
24. See Paul Gallo, op. cit., pp. 278–279.
25. See Gagné and Briggs, op. cit., p. 290.
26. See Gagné and Briggs, op. cit., p. 291.

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13

Final implementation

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Abstract: This chapter reviews the scope and impact of FDA regulations for the life sciences industry in general, and for training in particular. Any person who touches the regulated product, or who supervises that person, falls within the scope of the regulations. These persons must be trained on SOPs, insofar as they relate to the employees' functions, prior to their touching the regulated product. Thus it is critical that the final implementation of the training module includes all these employees. Next, a widely used approach to ensuring that employees are trained before they touch the regulated product is critically examined. A supervisor is required by SOP to ensure all necessary training and qualification requirements in the employee curricula are completed and documented prior to assigning an employee to a task. The shortcomings of such an approach are detailed, especially the failure to provide the supervisor with necessary information about the accuracy and currency of the employee curricula. Finally, an alternative approach involving a controlled document that includes a Target Audience List is proposed. This document facilitates the communication necessary to ensure the requisite training has taken place.

Key words: business owner, final implementation, individual training plan (ITP), just-in-time training (JITT),

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reinforcement training, re-training, Target Audience List, training curriculum, Training Outline, training to a procedure.

13.1 Introduction

The final implementation of a training module comes among the last phases of the program improvement model. A performance gap or a training gap has been identified in the corrective action and preventive action (CAPA) plan as a result of a revision of a standard operating procedure (SOP), and a carefully planned approach to address the gap was prepared. If management approves the design, the training program, including training materials and assessment materials, has been created in the development phase. These training materials and assessment materials are rolled out in a pilot implementation, a proof of concept study, highlighting the iterative feature of the program improvement model. In the case of a pilot implementation, the results of the program evaluation are fed back, closing the loop, facilitating further refinement of the training program. In the evaluation phase this is called a "formative evaluation." Further design and development efforts follow, until the module meets organizational needs. Then comes the final implementation of the module.

In this age of technological change, much attention has focused on the timing of training. On the one hand, training is optimally delivered close enough to task performance to ensure that the skill enhancement is still relevant but not yet forgotten. These requirements have led to just-in-time training (JITT), which has benefited from e-learning and other developments.[1] However, in the pharmaceutical, biopharmaceutical, medical device, blood product, and other

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FDA regulated industries, the need for optimal delivery of the training is constrained by the requirement that employees be trained before they "touch" the product.

At first glance, that requirement might seem to be trivial – just ensure that the training has been delivered "before," and be done with it. But the very dynamic of change that has driven manufacturing technologies as well as e-learning can create a climate of turbulence in process and procedure that makes ensuring "before" very dicey, and raises the prospect of serious compliance consequences if it turns out to be "after." The requirement that employees must be trained before they touch the product becomes especially acute in the case of final implementation of a training module, when it is no longer a matter of selecting the trainees as it is in the case of a pilot. Each and every employee impacted by a new or revised procedure must be trained. In this chapter we will examine that problem and consider several approaches to addressing it.

13.2 Scope and impact of FDA regulations

The FDA regulations for pharmaceutical manufacturing, set out in 21 CFR 211, are comprehensive in both scope and impact. Regarding scope, these regulations provide guidance for each person engaged in the manufacture, processing, packing, and holding of a drug product. The phrase "each person" includes both employees and supervisors.

The phrase "manufacture, processing, packing, and holding" is also comprehensive – it includes packing and labeling operations, testing, and quality control of drug products. In sum we can say the scope of the regulations includes any person who is (a) touching the drug product, or

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(b) supervising the persons who are directly touching the drug product.[2]

How do these FDA regulations impact on these persons? The regulations require that the pharmaceutical manufacturer develop written SOPs that provide guidance for a broad range of activities. These must be written procedures. As an example of the failure to meet this requirement, consider the FDA Warning Letter to Greer Laboratories, Inc., dated 24 June 2005: "Your firm failed to establish written procedures applicable to the function of the quality control unit."[3]

So a set of SOPs are required that will provide comprehensive guidance for dealing with the inputs, processes, and outputs of drug manufacturing, as well as quality control over this manufacturing. Not only are written SOPs required; the regulations insist the quality unit approves them – they are controlled documents – and the procedures be followed.

These written procedures must be followed. As an example of the failure to meet this requirement, consider the FDA Warning Letter to Intermax Pharmaceuticals, Inc., dated 13 May 2003: "Although your firm has a written procedure for training; it was found that these procedures are not followed."[4]

Moving from the general to the particular, the FDA regulations stipulate that all employees and supervisors be trained. 21 CFR 211.25(a) states that each person engaged in the manufacture of a drug product shall be trained:[5]

1. in the particular operations that the employee performs; and
2. in current Good Manufacturing Practices (cGMPs);
3. including the cGMP regulations in chapter 211; and
4. the dozen or so written procedures required by these regulations.

The scope of this training will "relate to the employee's functions;" the objective of this training will be "to enable that person to perform the assigned functions."

Moreover, 21 CFR 211.25(b) goes on to say that the supervisors of these persons shall be trained so as "to provide assurance that the drug product has the safety, identity, strength, quality and purity (SISPQ) that it purports or is represented to possess."

Three points follow from these stipulations. First, employees must have technical (or skill) training in their particular assignments. Second, the employees must have training in cGMPs that constrain the exercise of skills. Third, supervisors are responsible for the SISPQ of the drug product, and must be trained to fulfill that responsibility.

13.2.1 Training, or the lack thereof

How have companies within the scope of 21 CFR 211 responded to these requirements? We have reviewed the FDA GMP Warning Letters sent during the five-year period between January 2003 and December 2007.[6] There were 25 Warning Letters that mentioned deviations regarding aspects of 21 CFR 211 during that time period; they listed a number of observations that the FDA investigator had made during site visits to companies within the scope, including such issues as cleaning, contamination, sampling, etc. Seven of these Warning Letters (over 25%) also cited inadequacy of training, or inadequacy of the documentation of training – including inadequacy of skills training, training in GMPs, and supervisory training.

This pattern is not a historical anomaly; the FDA has been concerned about the adequacy of training in the pharmaceutical industry for some time. For example, regarding a somewhat earlier time period, FDA Senior

Compliance Officer Philip Campbell asked "Are the employees trained?" He further inquired "Are the supervisors trained?" Finally, he asked "Are there records of that training, and is it ongoing?"[7]

The fact that more than a quarter of these FDA findings point to problems in training should not come as a surprise. However, as we have seen, whenever there is a remediation (CAPA) for any deviation investigation or regulatory observation, that remediation will usually involve a revision of procedure or other controlled document, which in turn almost invariably involves training on the revised SOP. As Carl Draper, Director of the FDA Office of Enforcement, has put it, "The implementation of revised SOPs should include employee training."[8] So training will be the *indirect* outcome of a remediation, and will be the focus of some attention in the follow-up of the CAPA. Thus we expect that any Warning Letter – directly addressing issues of cleaning, contamination, lab work, sampling, testing, utilities, whatever – may also include a call for training, or for better training.

However, it seems that the FDA has come to expect ineffective training,[9] or inadequate documentation of training.[10] These expectations, along with the relative ease of assessing the occurrence and documentation of training via the ubiquitous tracking systems and learning management systems (LMSs), make the investigator's focus on these areas understandable.

13.2.2 Training versus "Re-training"

Recognizing the inadequacy of training does not amount to a call for "re-training." There is a substantial difference between training as an indirect outcome of a CAPA, and "re-training" as a *direct* outcome of an investigation, as a CAPA itself. Regulatory investigators quickly recognize the fallacy

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of "re-training" as a solitary or even major remediation.[11] For an example of such a fallacy, consider FDA Adverse Determination Letter regarding the Baltimore manufacturing facility of the American Red Cross, dated 27 July 2006. A Red Cross employee had not been trained before touching the whole blood product. When this problem was discovered two months after the event, the Red Cross conducted a root cause analysis (RCA) and concluded that this was a training problem, "The corrective action was to fully re-train all employees."[12] The FDA responded that "as a result of the incomplete investigation, [the Red Cross] failed to determine all root causes of the problem." (ibid.) The Red Cross was then fined more than $700 000.

A manufacturing unit is strongly inclined to release an impounded batch by declaring that the catch-all category "human error" was the root cause of the deviation or failure, and suggest "re-training" of the employee(s) as the corrective action. This is goal displacement;[13] it places the unit's goal, releasing the batch, above the organization's goal, which is identifying the root cause and implementing a remediation that will ensure the deviation will not recur. This goal displacement results in a false alarm, where re-training is the direct outcome of an investigation. The fallaciousness of re-training is amply demonstrated – re-training, re-training, re-training of the same employee(s), *ad infinitum*. As Philip Lindemann points out, "Not identifying the cause of failure may lead to additional failures."[14] The regulatory investigator will recognize this – as will upper management if there are metrics tracking CAPAs. The regulatory investigator, and upper management, will thereupon question the adequacy of the organization's investigations.

Moreover, if "human error" was proposed as the root cause of the deviation requiring "re-training," then the actual root cause would be:

- unreceptive trainee(s);
- inadequate training materials;
- an unprepared or incompetent trainer;
- ineffective interaction of trainee(s) and trainer; or
- some combination thereof.[15]

For none of these cases would remediation be as simple as "re-training," since the trainee would need to be motivated, the training materials would need to be revised, the trainer would need to be qualified, or the interaction would need to be enhanced before the remediation could go forward.

When John Levchuk calls for Reinforcement Training as a remediation for "future skills deficiencies,"[16] he indicates that refined or redefined training materials may be indicated, since "usually, only those skills most likely to be forgotten or suffer compliance erosion over time would be targeted for inclusion in a periodic reinforcement program."[17] Moreover, when he goes on to call for Remedial Training as a remediation for "acquired skills deficiency," he states that it would be "more appropriate and efficient if it were targeted to an incumbent's specific skills deficiencies." Thus Levchuk is not calling for "re-training" in either case.

In this part we have reviewed the scope and impact of the FDA regulations of pharmaceutical manufacturing in general, and of training in particular, and found them to be comprehensive. Any person who touches the regulated product, or who supervises someone who directly touches the regulated product, falls within the scope of the regulations. These regulations impact on these persons via written SOPs that provide comprehensive guidance for dealing with the inputs, processes, outputs, and the quality control of drug manufacturing. These employees must be trained on these procedures insofar as they relate to the employee's functions,

so as to enable that person to perform the assigned functions. As the process and procedures change, the impacted employees must be trained in a timely fashion. Hence the critical issues of timing attending the rollout of a finalized training module.

13.3 The typical organizational response

In many cases, an organization will realize that it must take further steps to ensure that employees are trained on the relevant SOPs before they touch the regulated product. Sometimes this is a result of a deviation investigation or an audit observation. Other times it may be the result of cost considerations, seeking to reduce rework and reprocessing, or because of compliance concerns. In any case, a typical response is to develop a new SOP that calls upon supervision to check the employee's training status. We will refer to such a controlled document as a "Task Assignment Procedure."

Such a procedure might require that the supervisor ensures all necessary training and qualification requirements have been completed and documented prior to permitting an employee to work independently. This check is typically performed by looking at the employee's training record in the validated tracking system or LMS during task scheduling. If employees have been trained on all the procedures listed in their curricula, the supervisor can make the task assignments.

What if the supervisor makes a mistake in checking the training records? What if the supervisor is not diligent, or overlooks a particular employee, or misses a page of the training record? Referring again to the Red Cross example, where the employee was not trained before touching the product, the Red Cross concluded that "the Education

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Coordinator failed to compare the employee's previous training transcript with the training requirements."[18]

Thereupon an organization might develop an even further SOP that requires periodic checks by the quality unit of a random sample of employees found in GMP areas at a given time, to ascertain if they are in fact qualified for their assigned job functions. We will refer to such a controlled document as an "Assignment Monitoring Procedure." If discrepancies are found, the Assignment Monitoring Procedure would require the generation of a Notice of Event (NoE) to inform management that a deviation has occurred. That NoE would need to address both the impact on the batch, to the extent the untrained employee had touched the regulated product, and the supervisory error itself.

13.3.1 Problems with this approach

There are two major problems with this typical approach. First, this approach presupposes that employees' training curricula and ITPs, listed in the tracking system, correctly and currently include the procedures that are relevant to the tasks to which the employees may be assigned. On the one hand, the curricula may not correctly reflect the procedures. How does a supervisor ensure that every single procedure that relates to this task, or this process – regardless of who the originator of the SOP may be – has been included in this curriculum? However, the curriculum may not reflect the current procedures. How does the supervisor ensure that the versioning up of each procedure has been the occasion for an update of the employee's curriculum?

These are hardly trivial questions. Change control and change management are substantial problems in a regulated industry subject to pervasive and persistent technological development. As if that were not enough, procedures are

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versioned up to change a single word. Procedures are versioned up and then found to be misaligned with higher corporate policies and standards; then they are versioned up still further to restore the *status quo ante* and alignment. Procedures are versioned up, omitting key paragraphs; they are subsequently versioned up to re-insert the omitted paragraphs. Multiple procedures co-exist for similar functions, for example, gowning; these procedures are versioned up, one by one, by their disparate business owners independent of each other.

The remedy for the constant revision of procedures is a combination of making better business cases for proposed changes, and having more peer review of the documents in process. But that remedy will not resolve the supervisor's dilemma of task assignment.

If the curriculum is either incorrect or not current, the supervisor cannot ensure the employee is adequately trained, no matter how diligently the training record is checked, no matter how carefully the Task Assignment Procedure is executed. The only way to ensure compliance in this case is by over-training, that is, by providing training to employees for whom the SOP may not be relevant. Of course, that is not cost-effective training.[19]

Moreover, over-training may result in employee resistance to training. Many times this occurs among high-performing individuals, say in a research institute, and presents special problems for organizational morale and productivity.

Second, assuming for just a moment that the curriculum is correct and current, this approach presupposes that recourse to a NoE is an adequate procedural response for supervisory error. Regulators typically find this unacceptable, because recourse to a NoE also requires a list of immediate and specific corrective actions that will be taken. As an example of the failure to meet this requirement, consider the FDA

Warning Letter to Pharmaceutical Formulations, Inc. dated 5 May 2004: "Process failures resulting in the rejection of substantial quantities of drug products were not investigated and there is no documentation to show any corrective actions."[20]

Returning to the first problem, it is crucial to recognize the misspecification of task responsibilities in the proposed Task Assignment Procedure. This procedure places the key responsibility on the supervisor for ensuring that employee training and qualification requirements are completed and documented, while not giving that supervisor necessary information about the accuracy and currency of the curricula, the status of procedure initiation, the status of procedure revision.

Instead, the Task Assignment Procedure should ensure that the originator (or business owner) of any new or revised SOP communicates with each impacted functional area to determine who the impacted employees are, that is, the training audience for the forthcoming SOP. This brings us to the third part of this chapter, where we propose an alternative approach to ensuring that the requisite training on the finalized module has occurred before the employee touches the regulated product.

13.4 The role of the target audience list

This part addresses four topics. First we will compare and contrast the purpose of a SOP with the purpose of training to a procedure. Next we will delineate the role of a Training Outline as a brief summary of the training implications of a new or revised SOP. Third, we will present a process map of the development and utilization of a Training Outline, and

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the associated Target Audience List. Fourth, we will discuss the use of the Target Audience List as the alternative approach to ensuring the requisite training occurs.

13.4.1 The purpose of a SOP

As already pointed out, a procedure lists the necessary steps (tasks) that, taken together, are sufficient to produce the desired process result. It can address several kinds of process – a person to machine process, a person to paper process, or a person to person process, or some combination of the three types. An SOP, typically in documentary form, indicates the sequence of tasks, the personnel or positions that are responsible for the tasks, and the standards that define the satisfactory completion of the tasks.[21]

13.4.2 The purpose of training to a procedure

Training is a person to person process that prepares each employee (the trainee) to successfully execute the steps (tasks) in a procedure, in the appropriate setting, stipulated order, mandated workgroup, and specified timeframe. Training is the combination of trainee(s), training materials, virtual or actual trainer, and the interaction of these elements.

Thus procedures and training are different. The procedure is a document, a controlled document subject to the quality unit's approval. Training is an interactive process. Of course, a procedure can be the object of training, and training can be proceduralized. But the two are distinct; reading a procedure is not the same as being trained on that procedure;[22] being trained on a procedure is not the same as being a subject matter expert on that process.

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How do we align the procedure and its associated training? How do we provide the supervisor with necessary information about changes to relevant procedures so as to ensure that employee training and qualification are completed and documented?

13.4.3 The role of the training outline

As discussed in Chapter 5, a Training Outline is a controlled document that provides a brief summary of the training implications of a new or revised procedure. The Training Outline allows any employee to quickly ascertain critical dimensions of training associated with a particular SOP, including the behavioral objectives of the training, the training module's fit in the larger curriculum, the delivery method, assessment materials, and of course the training audience.

When a performance gap or training gap is identified, management must decide on the appropriate CAPA to respond to the gap. There are two possibilities:

1. it involves a life-cycle document or documents; or
2. it involves non-life-cycle or GMP regulatory training.

In either case, the associated training will require the development or revision of a Training Outline. The instructional designer (or originator of the procedure) will ask "Does a Training Outline exist?" If one already exists, the Training Outline will be reviewed and revised as necessary. If not, one will be prepared.

The instructional designer will review five points:

1. Does the SOP or other document contain background history or perspective of the process that would aid in the training?

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2. Does the SOP or other document cover all related processes?
3. Does the SOP or other document thoroughly identify cGMP aspects?
4. Is all relevant training information covered in the Training Outline?
5. Will all facilitators present the training/information consistently?

In the case of non-life-cycle documents and GMP regulatory training, the instructional designer can ask management about the range of the training audience; usually it will straightforwardly be all employees, all managers, etc.

We display here a process map of the development and utilization of a Training Outline, and the associated Target Audience List, for the case of a life-cycle document (Figure 13.1). This will be followed by a brief discussion of the Target Audience List.

13.4.4 Developing and utilizing the Target Audience List

In the case of a life-cycle document, the instructional designer will review the SOP Scope Statement as well as the Task Responsibilities, and generate a provisional Target Audience List. This is the problematic case. These are the employees who must be trained to the new or revised SOP, based on the finalized training module, before they touch the regulated product.

The instructional designer will then attach the Training Outline, and the associated (provisional) Target Audience List to the procedure's Change Request. When the procedure and its Training Outline are circulated for review and

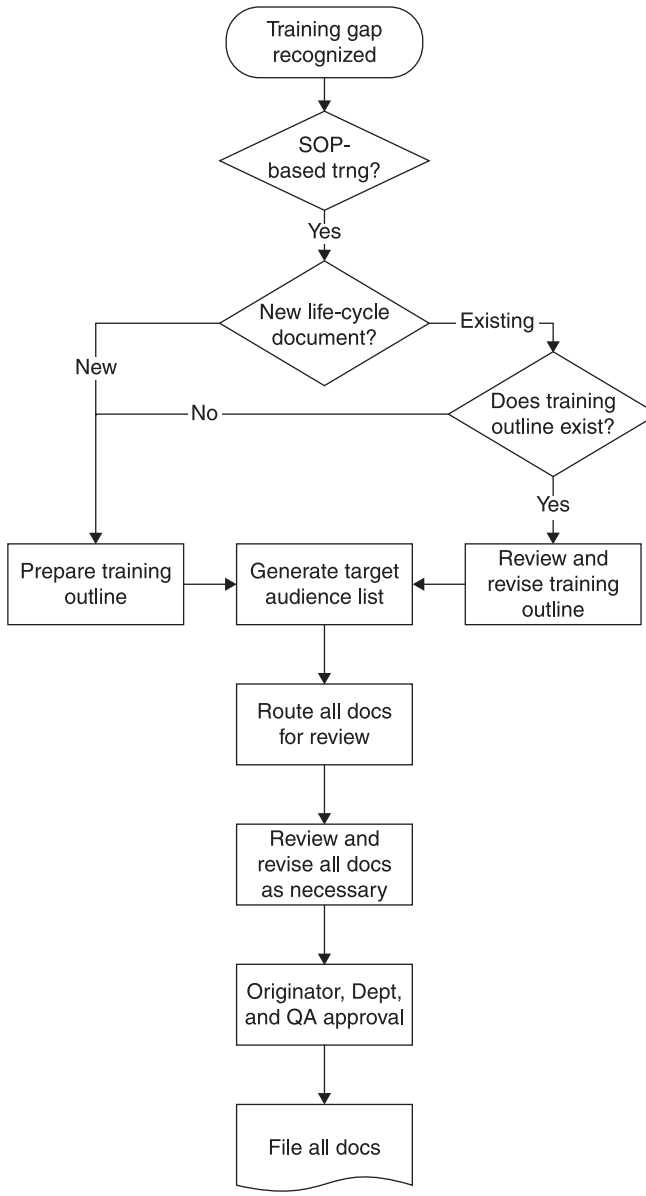

Figure 13.1 Training outline and target audience list

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approval, the Target Audience List will be circulated as well. Management of each unit impacted by the procedure will review the list and recommend limiting it or expanding it, based on their direct responsibility for the task assignments of the listed employees.

The instructional designer will then take those recommendations into account as the procedure, Training Outline, and Target Audience List are reviewed and approved. Moreover, management in the impacted units are alerted for the approval and implementation dates of the SOP, and can accordingly schedule personnel for necessary training on the finalized module.

After the new or revised SOP has been approved, there is a "training window" before the procedure goes into effect, a time period within which the impacted employees can be trained to the SOP. This window is typically a week or two in length. It is critical that the training audience be defined before that window opens, hence before the SOP is approved, so that all training on the finalized module will be completed before the implementation date.[23] Thus, the risk of untrained personnel touching the regulated product will be minimized.

13.5 Conclusion

This chapter had three parts. We first reviewed the scope and impact of the FDA regulations of pharmaceutical manufacturing in general, and of training in particular, and found them to be comprehensive. Any person who touches the regulated product, or who supervises that person, falls within the scope of the regulations. These regulations impact on these persons via written SOPs that provide comprehensive guidance for drug manufacturing. These persons must be trained on these procedures insofar as they relate to the

employee's functions prior to their touching the regulated product. Hence, the importance of ensuring that the final implementation of the training module includes all these employees.

Next we considered a typical organizational response to the need to ensure employees are trained before touching the regulated product. This takes the form of a procedure requiring that the supervisor ensures all necessary training and qualification requirements in the employee curricula are completed and documented prior to assigning an employee to a task. We pointed out several problems with this approach, especially the failure to provide the supervisor with necessary information about the accuracy and currency of the employee curricula.

Finally, we presented an alternative response whereby the Training Outline, a controlled document including a Target Audience List, is employed by the originator of a new or revised procedure to communicate with each impacted functional area to determine which employees require training. Those employees' curricula are revised to correspond to the new or revised procedure, ensuring they are trained on the finalized module before touching the regulated product.

13.6 Notes

1. See Carol Watson and Sanford Temkin (2000); Michael Jones (2001); and Bob Mosher (2005).
2. See 21 CFR 211.25, "Personnel qualifications."
3. Available from: *www.fda.gov/foi/warning_letters/archive/g5395d.pdf*
4. Available from: *www.fda.gov/foi/warning_letters/archive/g6159d.pdf*

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5. For biopharm personnel, 21 CFR 600.10; for non-clinical lab personnel, 21 CFR 58.29; for medical device personnel, 21 CFR 820.25; for human tissue recovery personnel, 21 CFR 1271.170.
6. Available from: *www.fda.gov/foi/warning.htm*
7. Cited in "Production Procedure, QC Unit Citations Top FDA-483 List," *Gold Sheet*, Vol. 38, No. 5 (2004), pp. 3–4. For FDA inspections conducted from 2001 to 2003, inadequacy of training was the seventh most cited observation, with 173 observations out of a total of 1933.
8. See the FDA Warning Letter dated 24 June 2005 to Greer Laboratories, Inc. Available from: *www.fda.gov/foi/warning_letters/archive/g5395d.pdf*
9. See John Levchuk (1990).
10. See David Gallup *et al.* (2003), esp. pp. 49–50 for an insightful discussion of FDA requirements for training documentation; also Vivian Bringslimark (2004), esp. pp. 51–52.
11. See James Vesper (2001), esp. p. 44.
12. Available from: *www.fda.gov/ora/frequent/letters/ARC_20060727_ADLetter.pdf*. See also Nicole Fuller (2006).
13. See Robert Merton (1957); also John Bohte and Kenneth Meier (2000).
14. See Philip Lindemann (2006).
15. As Levchuk, op. cit. has commented, however, "usually, available information is inadequate to establish a specific reason beyond failure to have a training program, failure to follow the written training program, or failure to ensure that personnel received training."
16. See Levchuk, op. cit.
17. See also Vesper (2001), op. cit., p. 46.

18. Available from: *www.fda.gov/ora/frequent/letters/ARC_20060727_ADLetter.pdf*
19. This is obvious for skill training; as Michael Swartz and Ira Krull (2004), esp. p. 906, have expressed it for training in cGMP regulations: "It is of little value to train or educate an employee on all of the regulations if there is no impact on the job that person fulfills every day."
20. Available from: *www.fda.gov/foi/warning_letters/archive/g4683d.pdf*
21. See John DiLollo (2000).
22. As Katherine Beauchemin *et al.* (2001), esp. p. 11, have accurately put it, "Clearly the 'read and understand' method does not meet the criteria set out for validity and reliability;" see also Bringslimark (2004), op. cit., p 46.
23. See James Vesper (2000), esp. p. 29.

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