"The Role of Critical Review in the Revision of Procedures," Journal of GXP Compliance, Volume 12, Number 5, Autumn 2008, pp. 77-89.

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This article 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 as an example of a laboratory weighing procedure and the development of a corrective action and preventive action project. Procedural changes in the example are evaluated and reviewed for US Food and Drug Administration compliance benefits. The management of change depending upon a risk assessment is considered.

INTRODUCTION

This paper considers the revision (the "versioning up") of a standard operating procedure (SOP). Revisions that add value to a procedure can contribute to best practices. Revisions that do not add value are wasteful, and from a regulatory standpoint suggest that a process is not in control. Given the ubiquitous changes in technology, procedures must be appropriately revised. The key word here is "appropriate." In order to ensure that the revision is appropriate, the SOP should be subjected to a critical review. Newly written procedures can also be subjected to critical review.

This article discusses a range of approaches to critical review of procedures, in terms of increasing credibility of the review findings. It is management's prerogative 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, consider how the management of change depends upon a 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, the increasing variability of the potency of an active pharmaceutical ingredient (API), is presented. 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 corrective action and preventive action (CAPA) plan is developed and implemented to remediate the facility and instruments; this leads to revisions to the relevant SOPs. It is necessary to critically review 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.

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

OVERVIEW OF CRITICAL REVIEW OF SOPS

An SOP is a "process control;" it controls the execution of a process. An SOP, typically in documentary form, indicates the sequence of tasks that make up a

process, the personnel or positions that are responsible for the tasks, and the standards that define the satisfactory completion of the tasks (1). The SOP lists the necessary steps (i.e., tasks) that, taken together, are sufficient to produce the desired outcome of the 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 some combination of the three kinds.

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 ubiquitous nature 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 that a process is not in control. In order to ensure that the revision adds value (i.e., adds that which 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," the US Food and Drug Administration 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.

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.

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 in the expert inputs.

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 subject matter experts, while clearly not the simple prejudices of laypersons, 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, 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.

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 (7). Typically, the approach to critical review of procedures that is selected will be part of a more general CAPA project.

This section discusses 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 (8). 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.

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:

- What might go wrong with the associated process? Answering this question involves *risk identification*.
- What is the likelihood that this will go wrong? A *risk analysis* addresses this second question.
- What are the consequences? How severe are they if this goes wrong? *Risk evaluation* provides an answer to this question (9).

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
- **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 (10).

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 (11). Using the following seven criteria, a laboratory test is graded for level of complexity by assigning scores of 1, 2, or 3 within each of the criteria:

- Knowledge
- Training and experience
- Reagents and materials preparation
- Characteristics of operational steps
- Calibration, quality control, and proficiency testing materials,
- Test system troubleshooting and equipment maintenance
- Interpretation and judgment.

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 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," (12) 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's Product Quality Lifecycle Implementation (PQLI) initiative has provided the following comments on the concept of criticality and its measurement (13). 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 (14).

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 (15). " Thus, the review must take into account the dimensions of complexity and criticality of the associated process.

Table I displays the dimensions of complexity and criticality.

TABLE I: Complexity and criticality of process.

		Criticality		
		Low	Med	High
Complexity	Low	A		
	Med		B	
	High			C

When the Complexity x Criticality is Low/Low (Scenario A in Table I), 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 x Criticality is Med/Med (Scenario B in Table I), 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 x Criticality is High/High (Scenario C in Table I), 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 discusses 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 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.

INVESTIGATING A COMPLEX X CRITICAL PROBLEM

FDA-regulated industry must have a written procedure that defines "events of concern," which includes 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 (16). These procedures were followed regarding the illustrative problem presented in the following example.

An Illustrative Problem

A quality control 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 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, subject matter experts, 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 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 QC's initial reports.

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 corrective action and preventive action plan 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.

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" (17). Such a system came into action as a result of the investigation into the illustrative problem presented in this paper. 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 versioning up the relevant SOPs, as well as associated changes in support of the laboratory procedure changes. Table II outlines the CAPA plan approved by management.

This section discusses 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 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 its use was also required.

TABLE II: 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 would be proposed as appropriate.
4.	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.

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.

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 guidances (18). The requirements included FDA's predicate rules for calibration and the documentation of calibration activities, and internationally recognized standards for calibration. The guidances included FDA's recommendations for a calibration SOP, and the directions to be gleaned from FDA's 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 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 (see Table III).

The process of calibrating equipment or instruments involves measurement standards, the calibration process itself, and the device. Measurement standards include the 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 (19).

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" (20). 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

TABLE III: 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.
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

referring to whether there is agreement between a measurement made on an object and its true (target or reference) value. Bias is a quantitative term describing the difference between the average of measurements made on the same object and its true value" (21).

Calibration weights are classified in accordance with the recommendations of the International Organization of Legal Metrology (22). Classes of weights include E1, E2, F1, F2, M1, M2, and M3, ranging from the highest accuracy weights (E1; maximum error at 1 kilogram 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) (23).

Speaking in general of a written procedure for the calibration of equipment, FDA has suggested (24) that the SOP include the sections listed in Table IV.

TABLE IV: Outline of SOP for the calibration of equipment.

Purpose and scope
Frequency of calibration
Equipment and standards required
Limits for accuracy and precision
Preliminary examinations and operations
Calibration process description
Remedial action for product
Documentation requirements

From a compliance standpoint, the eight topics listed in Table IV are important. FDA has made inspectional observations on organizations that have not adequately addressed them. As an example of the failure to address the frequency of calibration, and its GXP implications, see the FDA's Warning Letter to International Biologicals dated 12 June 1998: "There were no procedures outlining the frequency for calibrating the scales" (25). For an instance of not addressing required standards, see FDA's Warning Letter to BTI Filtration dated 07 Feb 2007: "your firm does not include the specifications for the equipment requiring calibration" (26).

For an example of failing to address limits for accuracy and precision, see FDA's Warning Letter to ChemSource, dated 15 Nov 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" (27). As an example of the failure to incorporate remediation steps in the alibration procedure, see FDA's 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" (28). For an instance of not meeting documentation requirements, see FDA's Warning Letter to Dale Dental, dated 14 Oct 2004, pointing out the "Failure to [ensure] that calibration records are maintained" (29).

The calibration procedure involved in the illustrative study presented in this paper was found to meet all these 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 discusses the review and revision of SOPs as part of the implementation of a more general CAPA project. It focuses 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.

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" (30). This calls for the testing of the efficacy of the changes made, 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 (see Table V).

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.

KEY POINTS

The illustrative study presented in this paper describes the critical review and implementation of changes to laboratory SOPs as part of a more general CAPA project. It further describes associated changes in support of the laboratory procedure changes. The changes described support a critical activity involving a commercial product. These changes require management approval, subject matter expert approval, and experimental data to support the change. The following key points have been presented:

- The change described impacted a critical activity affecting the accuracy of the determination of variability of potency of a commercial product
- A laboratory problem was identified as a possible cause of the problem
- A project team of personnel closely related to the problem was formed
- A comprehensive list of possible causes for the problem was developed
- Risk assessment was conducted for potential factors contributing to the problem
- Metrics were developed to characterize performance before and after corrective and preventive action
- The weighing procedure responsible for the problem was revised
- An associated procedure (calibration) was also revised
- Experimental data confirmed the success of the procedural change and associated changes
- Laboratory and calibration personnel were trained on the new procedures.
- Product potency data was monitored on an on-going basis to confirm the efficacy of the changes
- A document describing the above was prepared. This document was then affixed to change management documentation as supporting justification for the change.
- Document approval requirements included

TABLE V: 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. Statistical data treatment was described. • Other requirements. Training of calibration personnel and laboratory analysts on respective new SOPs was described. Additionally, 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.

management approval, SME approval, and supporting experimental data.

CONCLUSION

This article addressed changes to process as well as the revision of standard operating procedures. In order to ensure that the revision of the SOP adds value, it should be subjected to critical review. A 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's regulations for equipment calibration and the associated SOPs were examined. The internal calibration procedure for consistency with FDA requirements and technical quality was evaluated. 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.

ENDNOTES

1. See Welty, "Strategy and Tactics of Task Analysis," *Journal of GXP Compliance*, Vol. 11, No. 3, April 2007, pp. 27-28. 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, *Managing Food Safety*, College Park, MD: Center for Food Safety and Applied Nutrition (April 2006), p. 58.
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. FDA, *Guideline on General Principles of Process Validation*, Rockville, MD, CDER, May 1987, p. 4.
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, "Quality Management Systems: Fundamentals and Vocabulary," Geneva: International Organization for Standardization (Dec 2000), Sect. 3.8.5.
5. See William R. Shadish, Thomas Cook, and Donald Campbell, *Experimental and Quasi-experimental Designs forGeneralized Causal Inference*, Boston: Houghton Mifflin, 2002. See also James H. McMillan "Randomized Field Trials and Internal Validity," *Practical Assessment, Research & Evaluation*, Vol. 12, No. 15, Dec. 2007.
6. On the Rosenthal effect, see Robert Rosenthal, *Experimenter Effects in Behavioral Research*, NY: Appleton-Century-Crofts (1966); also his "Covert Communication in Classrooms, Clinics, and Courtrooms," *Eye on Psi Chi*, Vol. 3, No. 1, Fall 1998, pp. 18-22.
7. See, for instance, N. N. Radaev, "Setting Reliability Requirements for Products with Allowance for Economic Factors," *Measurement Techniques*, Vol. 47, No. 9, 2004, pp. 884-887.
8. As H. Gregg Claycamp has put it in his presentation to the CDER Advisory Committee for Pharmaceutical Science (ACPS), "ICH Q9: Quality Risk Management," Rockville, MD, CDER, 05 Oct. 2006,, 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 article focuses on quality risks.
9. See International Conference on Harmonisation (ICH), *Quality Risk Management Q9*, Nov. 09 2005, pp. 3-4.
10. See G.R. Kermode and S. Sivaloganathan, "Complexity Resolution for Design Excellence," in Sangarappillai Sivaloganathan and P.T.J. Andrews (eds.), *Design for Excellence*, NY: Wiley, 2000, pp. 387-388.
11. See 42 CFR 493.17. For an overview of CLIA, see Patrick Rivers, et al., "A Review and Analysis of the Clinical Laboratory Improvement Amendment of 1988: Compliance Plans and Enforcement Policy," *Health Care Management Review*, Vol. 30, No. 2, April 2005, pp. 93-102.
12. ICH, *Quality Risk Management Q9*, op. cit., p. 4.
13. See Roger Nosal and Tom Schultz, "PQLI Definition of Criticality," *Journal of Pharmaceutical Innovation*, Vol. 3, No. 2, 2008, pp. 69-78, writing on behalf of the Product Quality Lifecycle Implementation (PQLI) initiative of the International Society for Pharmaceutical Engineering (ISPE); also Thomas Garcia, et al., "PQLI Key Topics- Criticality, Design Space, and Control Strategy," *Journal of Pharmaceutical Innovation*, Vol. 3, No. 2, 2008, pp. 60-68. As Matthew Ferrier, "Risk Based Validation of Computer Systems," a presentation to the NJ Chapter, ISPE (June 15, 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.
14. See also Roger Nosal and Tom Schultz, op. cit., p. 70. David Fetterolf, "Developing a Sound Process Validation Strategy," *BioPharm International*, Vol. 20, No. 12, Dec. 2007, pp. 44-45 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 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 times or three times the normal operating range. If a parameter's operating range is less than two times its acceptable range, i.e. $r_o < 2 X r_a$, 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.

15. ICH, *Quality Risk Management Q9*, op. cit., p. 2. As Kevin O'Donnell and Anne Greene have expressed it in "A Risk Management Solution Designed to Facilitate Risk-Based Qualification, Validation, and Change Control Activities Within GMP and Pharmaceutical Regulatory Compliance Environments in the EU," *Journal of GXP Compliance*, Volume 10, Number 4, July 2006: "risk events can have multiple causes, with multiple associated risks, some less important that 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).

16. 21 CFR 211.192, "Production Record Review." See also Gamal Amer, "Corrective Action Preventive Action (CAPA): A Risk Mitigating Quality System," *Pharmaceutical Engineering*, Vol. 28, No. 3, May 2008, p. 67 on the "two types of quality events associated with risk."

17. See International Conference on Harmonisation, *Pharmaceutical Quality System Q10*, June 4, 2008, p. 9.

18. A similar critical review of the weighing SOP itself was required, but not included here. That review additionally took into account the guidance provided by *US Pharmacopeia* <1251>.

19. For instance, 21 CFR 820.72(b). See Andrew Lowery et al, *Medical Device Quality Systems Manual*, HHS Publication FDA 97-4179 (1996), Chap. 7, "Equipment and Calibration." According to the National Institute of Standards and Technology (NIST), *Handbook of Statistical Methods* (2003), Chap. 2.3. Available at:http://www.itl.nist.gov/div898/handbook: "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."

20. Lowery et al., *Medical Device Quality Systems Manual*, ibid.

21. See National Institute of Standards and Technology, *Handbook of Statistical Methods*, op. cit., Chap. 2.1.1.3. 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, *Medical Device Quality Systems Manual*, op cit, Chap. 7, "Equipment and Calibration."

22. See *Weights of classes E1, E2, F1, F2, M1, M1–2, M2, M2–3 and M3, Part 1: Metrological and technical requirements* (OIML R 111-1 Edition 2004), Paris: International Organization of Legal Metrology (2004)

23. 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."

24. Lowery et al, *Medical Device Quality Systems Manual*, op cit, Chap. 7, "Equipment and Calibration."

25. Available at www.fda.gov/foi/warning_letters/archive/1857b.pdf See also FDA's Warning Letter to American Blending and Filling dated 27 Sept 2001, pointing out the "Failure to establish written procedures for the calibration of compounding and laboratory equipment. instruments utilized in the manufacturing and testing of finished product are not calibrated on a routine basis;" available at www.fda.gov/foi/warning_letters/archive/g1833d.pdf

26. Available at www.fda.gov/foi/warning_letters/archive/b6289d.pdf
27. Available at www.fda.gov/foi/warning_letters/archive/g3695d.pdf
28. Available at www.fda.gov/foi/warning_letters/archive/g5817d.pdf
29. Available at www.fda.gov/foi/warning_letters/archive/g5014d.pdf
30. See Amer, "Corrective Action Preventive Action (CAPA)," op. cit., p. 72.

ARTICLE ACRONYM LISTING

API Active Pharmaceutical Ingredient
CAPA Corrective Action and Preventive Action
CLIA Clinical Laboratory Improvement Amendment
FDA US Food and Drug Administration
GLP Good Laboratory Practice
GMP Good Manufacturing Practice
HPCL High Performance Liquid Chromatography
ISO International Organization of Standardization
PQLI Product Quality Lifecycle Implementation
QC Quality Control
SOP Standard Operating Procedure
SMEs Subject Matter Experts

ACKNOWLEDGMENT

The author would like to thank his colleagues at various organizations—A.P., M.O., and R.R.—for putting this topic before him and suggesting approaches.

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