

Change Control Frequently Asked Questions and Answers

Sample Document

What is the most common or most serious deficiency noted by FDA investigators relating to change control?

FDA has issued a number of recent Warning Letters and 483 citations for inadequate assessment of changes. For example, a recent Warning Letter indicated that a change in production scale was not adequately evaluated prior to the change. The company did evaluate the potential change and conducted process validation. But, batch failures subsequently occurred because critical process parameters were not adjusted to accommodate for the larger scale process.

Another recent Warning Letter cited a firm for failing to recognize the need to conduct revalidation. In short, FDA expects that all changes be thoroughly reviewed by appropriate subject matter experts to identify ALL potential impacts of a change, then to construct a means to ensure that the change did not result in negative outcomes.

A key part of this pre-change assessment is to document the rationale for the change. One firm was recently cited for failing to document this rationale. When a clear rationale is provided, the firm (i.e., all reviewers of the change) has an opportunity for developing a greater understanding of how the change could impact other systems, equipment or processes. Bottom line... take the time to ensure that proposed changes are thoroughly reviewed, assessed and documented.

Is it necessary that the Quality Unit review all maintenance work orders? What is the purpose of this review?

On the surface, it may not appear that maintenance work orders would not be a source of potential change control concerns. After all, most maintenance involves restoration of equipment to its intended use or purpose. However, it is important to recognize that maintenance professionals are also "results oriented" individuals. When a key production line is down, they will usually resort to whatever potential repairs are necessary to restore production. Though this is not all bad, it can create change control concerns.

For example, let's assume a production packaging line is down because of excessive label rejects. The maintenance professional solves the problem by modifying the line rails to slow down the flow of labeled product through the labeler. This change would seemingly not impact product quality. BUT, in this case, the slower flow of product may impact the operation of visual inspection equipment or other qualified operations on the line. Thus, it is important that the Quality Unit review all of these routine and emergency maintenance work orders to simply ensure that a change thought to be innocuous, will have no impact on equipment operation and, ultimately, product quality. So, yes, it is important for Quality to review these

maintenance work orders to ensure that changes which may potentially impact product quality are properly assessed, controlled and documented.

I heard that FDA does not necessary accept that "like-for-like" changes need not be included in the change control program. Is this true? If so, what is the concern?

Most firms exclude "like-for-like" changes from their change control program. However, FDA and international regulators are becoming more and more skeptical of these changes. Let's look at one example... A pump on a spray dryer system must be managed to control product flow rate to the dryer. Because the product is sensitive to even minor changes in this rate, the pump is considered a critical element of the process. The pump recently failed. A new pump of the same model, same manufacturer and same design was purchased to replace it --- a like-for-like change. However, the new pump operates more efficiently than the "old" pump and generates 10% higher RPMs than the old one. Thus, product flow rate (i.e, injection pressure) is different and results in failing particle size distribution of the final product.

In this case, a like-for-like change impacted product quality. Thus, even for like-for-like changes, an assessment is needed to determine if pre-use testing, assessment, qualification or other verification is needed before use. In short, some truly like-for-like changes are innocuous and should be implemented without change control assessment. BUT, equipment, processes or controls that could impact product quality should receive additional scrutiny prior to use.

We use programmable controllers (PLC's) in our manufacturing environment. Do changes to the process made via these controllers need to be assessed through the change control program? Also, what about equipment using "recipes" that are programmed into the process?

Yes, all changes, including those for programmable controllers must be evaluated and managed if their operation controls product quality attributes. Typically, it is general practice to define at the IOQ stage whether a specific piece of equipment should be considered "qualified", thus, managed through the change control system. Then, when a PLC change is needed, you administer the change through your change control program for qualified equipment only.

As for recipe programs, these must be managed through the change control program if they control product quality attributes. For example, if a recipe is used to control the granulation process for a tablet product, any change to the recipe must be administered via change control. If the recipe is controlling the air conditioning in the office area, change control is not required. Investigators may also request a list of all individuals with security access to this equipment. When a number of individuals can make unauthorized and undocumented changes to the recipe, potential product quality concerns can result.

We have had this argument many times in our company.

Should we include changes in personnel (duties, work location, etc.) in the formal change control program or is management of personnel a responsibility of the area supervisor? What activities and documentation would the FDA expect regarding a move of an operator from one area to another?

Historically, changes in personnel were managed by the HR department and training requirements were the responsibility of the department supervisor. However, FDA is increasingly sensitive to the role that training plays in manufacturing operations, especially as technology has changed. When an individual moves from one manufacturing area to another, it is expected that you demonstrate an assessment for training needs, and that no activities are performed by this employee until training is successfully accomplished.

Firms are determining that the best means to ensure this occurs and is documented is to include such employee changes in the formal change control program. If the change control program is not used to document these changes, another system with similar assessment and documentation is needed.

What do you believe is the key emerging concern of FDA or international regulatory agencies regarding change control in pharmaceutical or medical device manufacturing operations?

I believe one of the key emerging areas of concern for regulatory inspections will be an assessment of how well we manage "productivity" improvements or when production volume significantly increases. One example of these improvements might be a downsizing event. FDA readily expects that we manage GMP operations to ensure we provide adequate and trained resources. However, during a downsizing event, responsibility for some of these activities shifts or could fall between the cracks. At least one international regulator has also commented on whether firms are properly staffing operations during production expansion.

In this age of economic concern, it is imperative that we properly assess these changes in operation and ensure that key activities are properly resourced. So, I do believe future FDA and international inspections will include a review of overall staffing, changes in volume, and how we have responded to these issues to continue to ensure GMP compliance.