IVT NETWORK
INSTITUTE OF VALIDATION TECHNOLOGY | an informa business
Unlimited Validation Knowledge Awaits...
Published on *IVT Network* (http://www.ivtnetwork.com)

CQV #2: "Like-for-Like" Change Problems

By **Alan M. Mancini**  , **Paul L. Pluta**

Jun 25, 2018 10:33 am EDT

The following is part of the Compliance in Quality and Validation (CQV) series which presents real-life stories reflecting compliance problems in the pharmaceutical, medical device, and related industries.

Readers are invited to contribute content, suggestions, comments, and ideas to improve this feature. All published content will be anonymous – there will be no connection to companies or organizations. CQV will be most useful when the quality and validation communities submit experiences that will help colleagues improve actual work situations. Please contact coordinators Paul Pluta atpaul.pluta@comcast.net or Melissa Carella atmelissa.carella@cbinet.com with content, comments, suggestions, or topics for discussion.

INTRODUCTION

This discussion addresses “like-for-like” changes in a pharmaceutical manufacturing plant.

Events described by validation and quality managers exemplify the subheading for CQV: “Do we really know what’s going on?” We think we know – but often we learn that we don’t. We feel that our policies are sound, our personnel are well trained, and they understand and follow procedures. But then a problem occurs. How did this happen? Why did they do this? Why weren’t procedures followed? What were our people thinking? Again, do we really know what’s going on?

Definition

Like-for-like changes are changes that are judged to not be a change that will affect the critical process parameters, critical quality attributes, or equipment functionality. For example, identical replacements of original equipment, disposables replacements, parts replacements, and similar usually inconsequential changes may occur without significant additional validation work.

Despite the apparent simplicity and straightforwardness of the above, validation and quality managers comment that like-for-like change problems are recurring and are often exasperating problems in their plants. Personnel erroneously claim changes to be like-for-like so no further work is needed. Do they really believe the change to be like-for-like, do they not understanding the potential consequences and impacts of the change, or do they simply want to avoid doing subsequent validation work?

“Like-For-Like” Problems

Validation and quality managers identified several types of “like-for-like” and associated problems –problems that should not happen.

1. Interpretation. The definition of like-for-like is often too-broadly interpreted. The rationale -- “This really isn’t a change” – has been heard by validation and quality managers numerous times. Some operators may make changes to optimize manufacturing; they honestly consider their changes to be insignificant. Other operators and mechanics define changes as like-for-like to avoid future validation work. Some claim to not know what constitutes a manufacturing change. Others assert that a slight change in equipment or in a process parameter is not really a change as long as it improves the process.

2. Equivalent equipment. Replacement with identical equipment is a straightforward like-for-like change. However, replacement with similar "equivalent" (not identical, but same function) equipment adds varying degrees of complexity to the like-for-like evaluation. Rationale for equivalency must be documented. Again, some personnel may erroneously claim equivalent equipment to avoid doing validation work.
3. Equipment installation. All equipment -- original, like-for-like, or equivalent equipment and parts – must always be correctly installed. Replacement of identical like-for-like equipment and parts may be problematic for reasons or emergency circumstances, 3rd shift work, or other reasons. Incorrect equipment installation may have serious product / process consequences. Correct installation of like-for-like identical or equivalent equipment must be verified and documented.
4. Documentation. Accurate and correct paperwork associated with all of the above is mandatory. If changes are made, associated document such as batch records, maintenance records, and qualification documents must be changed. If appropriate, justifications for not documenting same must be provided. Verifications of installations must be documented.

"LIKE FOR LIKE" VALIDATION PROBLEMS

Like-for-like changes should be of minimal consequence. However, validation managers comment that "like-for-like" issues are often among the most annoying problems in their plants. Some actual examples of unsuccessful like-for-like transitions provided by validation managers and quality managers from multiple companies follow.

Interpretation -- "This Really Isn't a Change"

Validation managers commented that "this really isn't a change" is a universal rationalization for minor process, parts, or equipment changes supposedly not requiring validation – they have heard this comment numerous times. For example, mixer speeds are increased to reduce manufacturing time, temperatures are adjusted to reduce reaction times, process times are reduced to increase manufacturing efficiency, and so on. Consequences of these "non-changes" include inadequately sealed packages, high variation in content uniformity and tablet weights, increased API degradation, high and non-uniform moisture content, and other undesirable process effects. Yet all are proposed to be "no change."

Shampoo viscosity. One manager reported hundreds of customer complaints on an OTC shampoo product. Complaints described the customers' hair becoming colored because the product colorant was concentrated in the bottom of the bottle. There were different shampoo colorants in multiple product formulations. When the consumer applied shampoo from the bottom of the bottle, they received excessive product colorant that in turn colored their hair. Dark blue colorant was especially troublesome.

The root cause of this problem was that operators reduced the manufacturing time required to sufficiently form the polymer matrix and mix formulation ingredients. They intended to improve plant efficiency by increasing through-put. This time reduction resulted in substandard liquid viscosity. When viscosity was too low, the suspended formulation colorants would settle to the bottom of the container. A deliberate change – not reported to technical staff and not even considered to be a change – caused numerous customer complaints and product returns -- and likely had serious effects on commercial sales.

Procedures vs. Performance

Validation managers comment that one of their most exasperating problems is changing operator mindsets regarding acceptable changes. Employees want to do a good job. They proudly say that they will "do whatever it takes to get the job done" which can subsequently result in a "production mentality" – a form of tunnel vision – a failure to see the bigger picture and impacts. Unfortunately, this mindset may not include exactly following procedures as part of doing a good job or failing to take into account the unintended consequences of the changes.

Alternate compressing machine. Another manager described an event in which the validated compressing machine for a specific product was not available. An operator decided to run the product on another (different company) machine. The respective machines were both qualified machines, but had different numbers of punches on the turret, a different feed mechanism, different control software, and other general design differences. The tablets were not able to be compressed on the alternate machine. While the operator's intentions were good, his judgment resulted in lost product, financial loss, and embarrassing CAPA documentation indicating terrible lack of understanding and control. The problem-solving investigation involved the operator response: "We didn't change anything – it's just another compressing machine." Machines may be validated / qualified and generally function in the same manner, but they are not interchangeable without prior development

and validation work for each individual product.

Equipment Installation

Equipment installation problems are another exasperating problem. In these cases, changed equipment may be identical, but was not correctly installed. After installation, the machine was not tested to confirm correct installation. When the machine operating direction is critical such as with airflow direction or rotation direction, results are usually significant and may be disastrous.

Laminar air flow in aseptic processing facility. One QA director described an incident in which routine revalidation of an aseptic filling line was being performed. All activities and tests were performed according to procedure including media runs, interventions, and so on. All results were acceptable and as expected until the filling line smoke test was conducted. The smoke test is intended to confirm the laminar air flow direction in the aseptic suite. All involved were shocked when the air flow was shown to be upward toward the HEPA filter instead of downward through the filter toward open product.

An investigation was initiated. Room and equipment history records were checked. The only activity performed in the area that could have caused this event was the installation of a “like-for-like” replacement blower motor by the site maintenance shop several months ago. Because this was judged to be a “like-for-like” change, only minimal documentation was considered to be required. Installation of the new motor was not tested. HEPA filtration of room air had thus been faulty for several months during which time multiple product lots were manufactured. These lots had passed all product testing and were released to commercial distribution.

FDA was notified. All lots manufactured during the time period when the blower motor was installed incorrectly were recalled. Aside from significant recall costs, this incident was highly embarrassing to the organization.

Mixer direction – Biotech manufacturing. Another validation manager described an event in which the cell growth and drug biosynthesis in a cell culture process was significantly lower than the historic average. Since this product was a high-volume product that was made in multiple tanks, the lower growth and production was not immediately obvious. As more low growth batches were manufactured, it became apparent that low yields were being consistently produced in one specific tank.

Equipment history records for the suspect tank were reviewed. The only work performed on the tank as documented in the equipment history log was the installation of a replacement motor on the mixer. The motor change was correlated to the first report of lowered growth and API synthesis. When operation of the tank was thoroughly investigated, it was found that the impeller was running in the opposite direction compared to the original installation and compared to other tanks at the site. Growth medium circulation was reversed relative to the original. This effect significantly altered the mixing profile of the cell culture, resulting in reduced cell growth and lower drug yield.

Documentation

Validation and quality managers described many incidents where documentation did not reflect reality.

Packaging batch records. A regulatory auditor was walking through the plant packaging area during the introductory tour of the GMP inspection. He asked to see the batch record from which the packaging process for a product was being done. While the line and machine type were consistent with the batch record, none of the process parameters were as specified – an obvious embarrassment and a terrible start to the audit.

Validation records. An engineering technician was assigned to complete five IQ and PQ protocols on five identical milling machines. The first machine was successfully completed. Machines #2 and #3 were completed a few weeks thereafter. When requested to present the original data for machines #2 and #3, the technician submitted machine #1 data. His response: “The machines are all the same. There is no need to repeat same testing on all machines”.

What and Why?

In each of the above events, a perceived “non-change” was performed without confirmatory testing. Process time was changed, alternate equipment was used, equipment was not correctly installed, or there was a general lack of understanding of like-for-like change. All were implemented without asking questions or thoroughly completed the change project. We assume the intentions of the personnel involved were good, i.e., save time, save, money, resume processing, work quickly, and so on. However, the consequences of these omissions were significant both in GMP compliance and financial losses. The laminar airflow problem was especially serious involving FDA and a significant recall.

PROBLEM RESPONSES

Validation and quality managers identified several issues to be addressed in response to like-for-like problems. Some of these are typical responses to FDA 483 observations and warning letters.

Change Control Education and Training

Training in change control is an obvious need in all of the above examples. Managers commented that “old habits die hard.” Personnel who have been functioning with an apparently desirable attitude (“…do whatever it takes.”) are not inclined to simply follow procedures and report when procedures are inadequate. A “procedure” orientation is needed. This is not accomplished by one or two training sessions. Verifying correct installation must be included in like-for-like equipment changes.

Site Review and Approval

Validation managers agreed that like-for-like changes should ultimately be evaluated by the site Validation Approval Committee (VAC). Having all changes reviewed by the VAC standardizes evaluation and decision processes. Changes would then be evaluated as either requiring validation or appropriate lesser like-for-like documentation.

Documentation

Managers commented that validation documentation for like-for-like changes is often too extensive causing people to erroneously invoke a like-for-like judgment – and avoid doing any documentation.

One manager suggested an alternate approach to minimize like-for-like documentation. A simple written memo with appropriate review and approval attesting to correct installation of identical replacement equipment is sufficient in place of a protocol. The memo should include a statement that identical equipment was installed, installation was correct, and operation was confirmed by a second individual. The memo should be approved by management of the responsible group (e.g., maintenance, engineering, others) and site QA. The approved memo would then be filed with the validation request to close the “like-for-like” activity. This approach was successfully implemented by one validation manager with very positive results.

Emergency Changes

In some organizations, maintenance management has final and complete authority to judge whether validation of a change under their auspices is required. This practice should be limited to initiation of emergency changes only. If an emergency change is like-for-like in the judgment of maintenance management, the emergency work should be initiated as soon as possible. Work should then be documented in equipment history logs or other site documentation systems. Completed emergency changes should then be evaluated by the site VAC. Appropriate confirmatory work, if necessary, could then be prescribed. Acceptability of all changes should be the ultimate responsibility of the VAC.

FINAL THOUGHTS -- ORGANIZATIONAL CULTURE AND MANAGEMENT

The events described above are ultimately a management problem. To be successful as managers and for their organizations, managers must strive to establish a partnership culture with employees. Managers must become activity engaged with operators, maintenance, and QC/QA personnel.

To really know what’s going on depends on employees who identify and communicate problems to management, ask questions, and want to do the right thing – and believe management and staff are all in this together. Repeat training, reading policies, and revised procedures will only go so far. To really know what is going on, managers must treat employees as colleagues, encourage communication, explain approaches, and answer questions – working with their people. Management must proactively address problems with colleagues – these are our problems that we must solve. Developing a partnership culture based on trust between management and colleagues will do much to solve like-for-like and other problems – and you

will know what's really going on.

ABOUT THE AUTHORS AND COORDINATORS

Paul L. Pluta, PhD, is a pharmaceutical scientist with extensive pharmaceutical industry and university academic experience. He is also Editor-in-Chief of the Journal of Validation Technology and the Journal of GXP Compliance. He may be contacted at paul.pluta@comcast.net.

Alan M. Mancini, RPh, is a pharmacist with substantial experience with formulation, process, and package development, scale-up, technology transfer, validation, and optimization of pharmaceutical dosage forms on a global basis. He also has university academic experience. He may be contacted at amancini1@comcast.net.

Melissa Carella is Managing Editor of the *Journal of Validation Technology* and the *Journal of GXP Compliance*. She may be contacted at melissa.carella@cbinet.com.
