

2010

Rational Revalidation

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Publication Details

Aleem, H., Edwards, R. & McCarthy, T. J. (2010). Rational Revalidation. *Journal of Validation Technology*, 16 (2), 83-92.

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The economic problems the world is currently facing have resulted in severe reductions in capital investments, hence a drive for retrofit to increase efficiency and make the most of existing assets.

Although this is the case in many industries, what compounds the situation in the pharmaceutical industry is the slowdown in development of new drugs. This has led to alternative strategies such as outsourcing R&D to Universities and small Biotechs. Unfortunately new approaches based on “omics” and “Systems Biology” have not delivered any breakthroughs yet. Furthermore, on the factory floor, novel technologies such as Process Analytical Technology (PAT) and continuous processing have not become main stream yet as they require specialised knowledge and expertise that is not readily available except possibly to the large pharma companies.

Recent regulatory fines of some manufacturers, price controls in Europe and the uncertainty regarding Health Care reforms in the US compound the situation even further.

All the above call for integrating the economic issues with the technical ones in the operations of the pharma industry. A major issue in the industry is assessing and managing risk to the product, as for example in ICH Q9 [1]. In the current economic climate however, the scope of risk should be widened to include risk to the business as well. Without a business there won't be a product for which to assess the risk! The original quality standard ISO 9001 of 1987 is an example of a quality management system implementation that did not take economic factors into account. It became a bureaucratic burden that did not deliver its full potential, a situation which was subsequently rectified in the 2000 version.

In this article we consider one of the costly aspects of pharmaceutical operation, that is validation, in particular revalidation which will become exceedingly important in view of the decline in capital investment in the current economic climate as mentioned above.

We start by giving justification, i.e. why we may need to revalidate a system. Next we outline a strategy to prioritise among the systems to be revalidated and to decide on what to revalidate, how and when. We then consider how to identify the need for revalidation and to reduce this need. Next we discuss the costs associated with revalidation, and finally the different business models for approaching the problem. Throughout we attempt to integrate the business decisions with the technical ones in a pragmatic way. Having said that, we should make it absolutely clear at the outset that this does not in any way mean compromising product quality or patient safety, as those are a given in the pharma industry for ethical and regulatory reasons, in addition to business ones as well (corporate image and avoiding litigations).

In our context, we will use the term system in a broad sense to incorporate the process, the equipment on which it is implemented and the procedure to

follow in executing it. We present our case with secondary drug manufacturing in mind.

Why revalidate?

It is not uncommon in the pharmaceutical industry to view validation as a one-off activity to be performed once, and not to be revisited unless a major change to a system takes place. In fact, validation should be regarded as a state to maintain rather than an activity to perform.

There are several reasons for revalidating a system (Figure 1), the most compelling of course is that it is often a regulatory requirement. Regulatory authorities mandate revalidation after a change to a process (including equipment, instruments, procedures and methods) that may impact product quality. The European Union (EU) GMP in addition, refers to periodic revalidation irrespective of such change [2]. Indeed, chapter five in the EU GMP entitled "Production" states that "*Processes and procedures should undergo periodic critical re-validation to ensure that they remain capable of achieving the intended results*". Furthermore, Annex 15 of the same GMP entitled "Qualification and Validation" states that "*Facilities, systems, equipment and processes should be periodically evaluated to verify that they are still operating in a valid manner*", although this requires only an evaluation of the validated status of a system, if this leads to unacceptable results revalidation may be expected.

Periodic revalidation is also required by the World Health Organisation (WHO) guidelines on GMP [3]. Annex 4 of the WHO Good Manufacturing Practices entitled "Supplementary guidelines on good manufacturing practices: validation" states that "*There should be periodic revalidation, as well as revalidation after changes*". The fact that the WHO is an international body (as opposed to a multinational one such as the EU or PIC/S) indicates a degree of worldwide consensus especially outside the ICH countries.

Possible Drivers for Revalidation

- **Changes in the process**
- **Changes in regulations**
- **Changes in regulatory expectations of current regulations**
- **Changes in industry or company best practices**
- **Maintaining an updated view of the process, audit readiness.**

Figure 1: Possible drivers for revalidation

Other regulations introduced in the past such as the FDA 21 CFR Part 11 addressing electronic records and electronic signatures, necessitated the revalidation or at least the assessment of legacy systems that were in place before such regulation were introduced. Given the changing nature of technology, it is not unreasonable to expect further changes in regulations in the future that may cause revalidation of existing systems. PAT is an example of such a technology; depending on how PAT is utilised (monitoring and data collection vs integrating into a control loop), this may result in redefinition of the process and hence necessitating revalidation.

Another reason for revalidation is the change in regulatory expectations even when the regulations themselves do not change, which often manifests itself in the change in focus of regulatory inspections. This is also evident in the changes and updates to existing guidance documents by regulatory authorities or the introduction of new ones. A prominent example of that is again the change in regulatory expectations with regard to the implementation of Part 11 even though the regulation itself did not change [4]. Indeed this has also been the case with validation altogether over the past three decades. Changes in regulatory expectations can also be inferred from warning letters or comments from pre-inspection assessments by regulatory authorities. It should be noted that the recent FDA draft guidance for process validation [5] has removed the explicit reference to revalidation that was in the original 1987 guidance document. Instead, it suggests a system life cycle approach that incorporates “continued process verification”, which in essence is validation maintenance.

Changes that occur in the practice of validation in industry may cause a firm to revalidate its systems to align itself with current best practices. The introduction of the ISPE Baseline Guide 5: Commissioning & Qualification and its impact on the way qualification is performed in industry is an example of that [6]. Such concepts as impact assessment and enhanced design review have become more formalised and common place with the introduction of this guide. This does not necessarily mean repeating the whole validation exercise but possibly only producing the aforementioned documents in retrospect as an aid for future change control.

The issues outlined above related to regulations and industry best practices, can be regarded as external to a firm in the sense of being beyond its control. In contrast there are other causes for revalidation that are considered internal to a firm. For example in the case of mergers and acquisitions, the standards and practices of validation may differ between the organisations involved and revalidation may be desirable to align them together, especially if an existing facility becomes part of a global organisation with established standards. In addition there are the usual causes for revalidation such as following a change that may impact product quality, and to maintain a validated status of a system.

A further motivation in assessing the validated status of a system is the benefits accrued from such an endeavour, especially from a business perspective. These include taking a snapshot of the status of the different

systems and updating it regularly thus maintaining a current view of the process and keeping it under control ensuring that it is always in an audit ready state. This update may merely involve updating the documentation and does not necessarily have to entail a full-fledged testing regime.

Setting a revalidation strategy

Once the need for revalidation has been identified, a strategy has to be formulated for carrying out this task, in particular to decide on what to revalidate, how and when.

What to revalidate?

Clearly all systems with potential impact on product quality must be kept in a validated state at all times. When revalidating such systems, constraints on resources including time, cost and expertise make prioritisation in the order of revalidation inevitable. The first step is thus to prioritise among the different systems needing revalidation.

The common approach is to start with systems used for parenterals, followed by those for other less critical products such as orals then topicals. However, we believe that the prioritisation should also include a business aspect, i.e. systems that produce products that are critical for the survival of the business such as blockbuster drugs. Producing a parenteral that is not financially viable while ignoring a less critical yet profitable product will mean that eventually production of the former will not be sustainable and potentially neither will be the business as a whole.

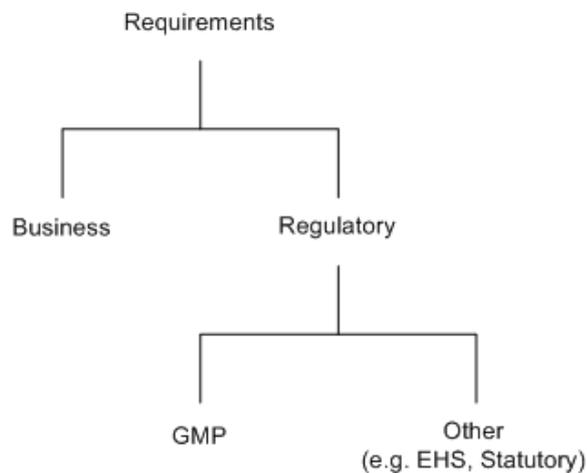
Needless to say, all products are required to be manufactured with robustly validated processes, however, when resources are limited there are short term alternatives to revalidation (Figure 2). One such alternative is to temporarily discontinue production of one product until revalidation of other more financially viable ones is completed. A second alternative for a multi-site firm is to transfer production to another site that does have the resources for validating the process. A third alternative is to temporarily continue production but with additional procedural controls such as 100% inspection, additional in-process controls and more frequent product reviews. This is similar to the case of manufacturing Active Pharmaceutical Ingredients (API) for investigational products as outlined by the ICH GMP Guide for API Q7 [7]. In the unlikely event that none of the above options is attainable, production can be contracted out. It should be emphasised however, that those are only temporary measures and are not meant to replace performing the required revalidation exercise, unless of course moving a product to another site, contracting it out or possibly licensing it or even selling the intellectual property right (IPR) to another manufacturer is part of the firm's strategic objectives. It should also be noted that these options can apply to the original validation as well

Temporary Alternatives for Revalidation

- **Discontinue production until revalidation is ready**
- **Transfer production to another site within the organisation capable of validating the process**
- **Impose additional procedural controls (such as 100% inspection)**
- **Outsource manufacturing**

Figure 2: Temporary options for a process awaiting revalidation

Having decided on the order in which the different systems will be revalidated, next comes prioritisation within a system (figure 3). This means deciding on which functions and features within a system to validate. Such decisions will likely be different from those of the original validation. It is not uncommon, especially in turn key projects that contractual and Health and Safety issues be addressed as an adjunct to the validation exercise as this is more convenient and cost effective for the contractor, in effect all forming part of commissioning. This however, need not be the case in revalidation.



Prioritisation within a system

EHS = Environmental, Health & Safety

Figure 3: Prioritisation for revalidation

The requirements to be verified for any system can be classified into two main categories business requirements (for example capacities of lines), and regulatory requirements (Figure 3). The latter in turn are further classified into

GxP requirements and others including Environmental, Health and Safety (EHS), and statutory. We believe that in the case of revalidation, only GxP requirements are to be verified. This does not mean that other regulatory and business requirements are not important, it only means that those while still need to be verified, are outside the scope of the revalidation exercise.

How to revalidate?

Now we turn our attention to the extent revalidation is to be performed, i.e. setting the acceptance criteria by which to judge the process. In a new project, and when ordering new equipment the full extent of its usage is not always known before hand. Specifications are thus set both for current and expected future usage. Factory acceptance testing (FAT), Site acceptance testing (SAT) and indeed validation, often test against such specifications that in many instances correspond to the performance limits of the equipment. One of the purposes of that is to ensure that contractual obligations on the supplier are met. In revalidation however, the purpose is to test an existing process against known requirements that may be in a much narrower range than that of the equipment operating range.

Revalidation should be against the current process requirements, if those do not formally exist then a “realistic” user requirement specification (URS) should be drawn in retrospect as a starting point. This should be tested against, rather than the full range of the equipment specifications. Examples of such a case include a mixer that is operated at certain speeds that are less than its maximum possible. In such a case there is no point in qualifying this maximum, which is not employed in the process and may possibly be unachievable, especially if the equipment has been in operation for many years. Similarly, line speed for a packaging line for example or speed of a depyrogeneration tunnel that is known to operate at a speed much slower than its maximum to guarantee performance. Another example is for autoclaves that normally include several types of sterilisation cycles only a subset of which is utilised, hence no need to try to validate the performance of all of them. It is of course important to emphasize in the validation report the parameters for which the system is validated, in case the equipment is needed in the future for a different process.

Thus in revalidation, the purpose is to verify process requirements rather than other engineering requirements such as throughput or capacity, as meeting these does not guarantee meeting product specifications. The problem of loss in throughput will still need to be addressed albeit on a more strategic level than that of revalidation, such as site capacity expansion or major equipment overhaul.

When to revalidate?

According to all GMP regulations, any change with potential impact on product quality must be assessed, with revalidation as a possible outcome, indeed this falls in the realm of change control. Additionally, as outlined in the EU GMP and the WHO guidelines, this assessment should be carried out periodically. We look at those issues here and try to put them in a unified

framework. We classify the need for revalidation into time based and event based (Figure 4).

Change control

Event based revalidation essentially refers to revalidation following a change. This change can be either inadvertent or predetermined. The former means that the change has to be performed in order to be able to keep producing the concerned product with the required specifications. This can be the case for example when a part with impact on product quality malfunctions and has to be replaced. This kind of change is in essence unplanned.

Another example is when a change in regulation causes a part to become unsuitable for production even if it is functioning correctly, possibly due to changes in material certification requirements. In such a case the replacement will have to be revalidated if the original part was deemed GMP critical. In this sense a firm does not have the choice of not performing the revalidation, hence we term it inadvertent.

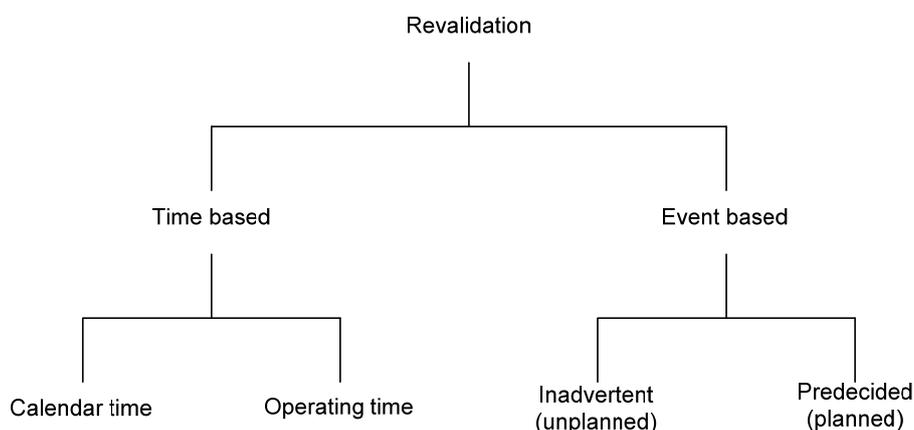


Figure 4: When to revalidate

Predetermined changes on the other hand are planned ahead of time. Those can be further classified according to the purpose into reactive and proactive. The former are changes in reaction to a recurring problem, which, while not causing stoppage or non-conformity, may cause repeated product problems in the long run. Proactive changes are ones whose purpose is to improve the process without it currently suffering any problems. This improvement can be for example to narrow product variability in spite of being already in spec, or for technical improvement like replacing a machine part with a more efficient one. It can also be for purely economic reasons such as increasing throughput or reducing energy consumption. Such proactive changes can fall under process optimisation, be it the production process or the business process. Those would naturally take lower priority than unplanned changes whose purpose is to keep production going and maintaining product quality. In either case, whether the change is planned or unplanned, a rigorous change control procedure should be in place. For the planned changes, this should stipulate the assessment of the change and its impact on product quality and process integrity in addition to health and safety issues when

necessary, before the change is implemented. This will ensure not only that the resulting system after change is compliant, but also that other processes are not affected while the change is taking place. An example of this is when modifications are made to a hall or a building that houses other systems, or to utility lines that feed other processes. Such change control procedures would also ensure updating documentation and records post modification. Similarly for unplanned changes.

Sterilisation and aseptic processes

Time based revalidation, as is evident from the term, is performed periodically and is most common in aseptic processing and sterilisation. It is required by the WHO guidelines on GMP. The timing can be based on operating time or calendar time. The choice of which approach to take is based primarily on the risk to product quality, in addition to economic factors. Most commonly in validation a calendar-time based approach is taken because it is easier to plan and implement, however, this is not necessarily always the best choice from an economic point of view. Consider the case of a system that is rarely used due to low demand on its product. It may not be economically sound to validate it periodically in spite of the low utilisation as there is potential for it not being used between two consecutive validations. On the other extreme, there is a system that is in continual usage possibly on shift basis, for such a system taking a purely calendar-time based approach can be too risky. If at revalidation the system was found to be in significant deviation, this would jeopardise the entire product that has been produced since the last successful validation. In such a case revalidation based on the number of batches produced may be safer both to product quality and economically. Thus in practical terms and to reduce the risk to product quality, in this particular case the shorter of both times should be taken.

The idea of operating time based actions is common in preventive maintenance programmes whereby different parts are replaced after certain hours in operation. In validation this corresponds to the number of batches produced.

The essence of this section is that the choice of when to revalidate, whether it is event based (planned or unplanned change) or time based (operating or calendar time) is that it should ultimately be based on potential risk to the product.

It is worth mentioning that the concepts of time based and event based actions come from the field of programmable control, where time based refers to timers while event based refers to counters, activation of limit switches or other conditions. Strictly speaking one can consider time based actions as event based ones whereby the elapsing of the time period is itself the event. However, the convention has been to treat them as distinct and we follow this convention.

How to identify the need for revalidation and reduce it?

Ultimately one can argue that the need for revalidation arises due to the occurrence of a change. This change may be known and decided, whether planned or unplanned. Alternatively, it can occur without being detected, which time- based revalidation attempts to mitigate [3], as waiting for the

change to manifest itself in an out of specification product is too late from both quality and business points of view. Hence to take a more structured approach, there should be mechanisms to detect and if possible predict this change as soon as possible (Figure 5).

Such mechanisms already exist in practice although not always tied to validation, a powerful one of which is Statistical Process Control (SPC). SPC allows the continuous monitoring of the process and can detect early on, gradual shifts from its current (ideally controlled) state. The basis of SPC is to maintain the process in a state of “statistical control”, meaning that its only variability is due to “chance causes” and does not include any “assignable causes” [8]. Hence when an SPC chart detects an out of control condition, this signals that a change has occurred and should prompt investigation that may lead to revalidation. It should be noted that in the statistical sense, an out of control condition does not necessarily mean an out of specification product, however, such a condition if not addressed may lead to a non-conformity. Thus SPC serves as an early warning against non-conformity. There are variations on SPC that make it more discriminating in diagnosis and hence a more powerful tool, one such extension is Multivariate SPC (MSPC) [9]. SPC is a convenient tool and can be implemented at minimal cost as many modern systems include the required functionality as standard. This includes data gathering and processing such as calculating means, standard deviations and control limits. Examples of such systems include modern tablet presses and tablet autotesters. When applying SPC however, one should be aware of its underlying assumptions and consequently its limitations.

Another mechanism that is currently used is the Product Quality Review which has to be conducted periodically as mandated by the GMPs. As part of this exercise according to the EU GMP “*A review of critical in-process controls and finished product results*” should take place, in addition to a host of other reviews [2]. Such reviews would detect any major deviations in the process and would hence trigger an investigation that may lead to revalidation of one or more of the systems associated with this deviation. Such a product quality review already takes place on regular basis and hence will not constitute any additional cost. Naturally the usefulness of this exercise in detecting the need for revalidation early enough depends on the frequency with which it is conducted. As with the case of periodic revalidation, risk to the product is a factor in the choice of the review period. The common practice at present is that it is conducted annually for most products.

To reduce the need for revalidation (Figure 5), a firm should ensure the timely execution of effective preventive maintenance plans. This will help keep equipment at a high level of performance, hence reducing its variability and reducing problems with the processes utilising it, and subsequently the need for revalidation. Another important factor that contributes to reducing this need, is strictly executing the calibration plan. It is the measuring instruments and devices that detect any deviations from specifications. Thus, the reliability of the decisions based on their results including the costly decision to revalidate a system, will depend on the accuracy of those measurements.

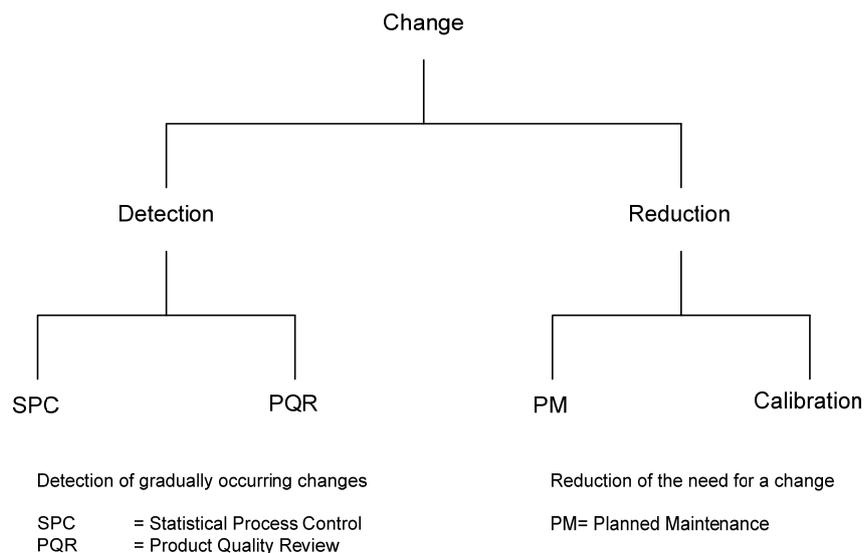


Figure 5: Some means for detecting the need for revalidation and reducing it

Costs associated with revalidation

We now focus on the business aspects of revalidation, these include its cost and the alternative business decisions associated with it. In this article we attempt to rationalise the revalidation process in the wide sense including aspects of its management process.

The most costly phase of revalidation is when performing it for the first time. This is especially so for systems that have been in operation for a long time as there is potential risk of drifting from the original validated status. The high cost of the first revalidation for such systems is due to two main reasons. Firstly some aspects of the validation status may either be not known or cannot be verified, and hence there is a potentially large cost involved in the assessment of this status. Secondly, a system may have approached a point where the cumulative effect of minor changes increases the risk of it becoming sufficiently deviated from its initial validated state that the cost of bringing it back into this state will be high. We look at those two costs (Figure 6).

Cost of assessment of the validation status

The major contribution to the assessment cost is the difficulty in locating the necessary information about a system, in particular about the equipment used in the process. This may be due to a piece of equipment being so old that its documents may have been misplaced or possibly lost altogether. Such important documents include validation files with all the supporting certificates and reports, and possibly even operation and maintenance manuals for a machine. Another cause for this difficulty is the case where a machine has been relocated from another site but not all the documents have been relocated with it or were lost in transit. Or they may be available but in a different language as is the case of a firm having plants in different countries. Those scenarios are not unrealistic in light of the many mergers and acquisitions that overtook the industry in the past decade, with the

subsequent close down or downsizing of plants in different locations. The time taken to locate documents and information is time taken off production and hence indirectly translates into financial cost. In addition there are the direct costs associated with the validation personnel involved in this assessment.

Cost of performing the revalidation

This is the cost of actually performing the tests, recording the results and reporting the conclusions, in addition to taking the equipment and systems out of production. However, there are other costs associated with this issue.

Due to the potential loss of documents mentioned above, some of those will have to be reproduced. This can be a lengthy exercise, as depending on which part of the validation lifecycle has missing documents, the situation can involve a major revalidation exercise including generating a URS.

Even if all the documents are available, for an old piece of equipment the change in regulations or regulatory expectations outlined earlier may necessitate obtaining additional data that was not required in the past. This is especially so with processes that were controlled with legacy computer systems and where source code availability was not a requirement, or equipment that has product contact parts or lubricants that were acceptable in the past but are not any longer. Obtaining such data can be a challenge because a supplier may not be in business anymore or the particular model in question may have been discontinued and no documents relating to it can be issued. Yet in another scenario, the equipment model may still be in production by the supplier but certain information about it is not available or is not normally generated by the vendor to begin with. This is not an uncommon case with suppliers for whom the pharmaceutical market represents a small share of their overall business. Again such missing information will have to be generated by the pharmaceutical firm and can be very costly, such as the case with positive material identification.

In addition, there is of course the cost of actually performing the revalidation tests even if all the necessary information and documents are available; this includes the time, labour, instruments, and the product or placebo if required. Finally, as in the case of assessment costs, there is the cost of lost opportunity, i.e. the time that the equipment is out of use and the personnel are taken off their regular jobs.

Based on the above costs, in conjunction with the historical data about the performance of a given process in addition to the possible lack of support from equipment suppliers, a decision can be made about what to include in the revalidation programme. For example, if in-process data and the regular Product Quality Reviews indicate a recurring problem from a given piece of equipment, and in addition this is coupled with missing or unobtainable data to verify its performance, then it might be more cost effective to replace it altogether. This will save the time and costs involved in assessing the state of this equipment and bringing it up to the current expectations with respect to validation standards. In a wider context, this would apply to all the systems on site needing validation and can help to narrow down the prioritisation process mentioned earlier. More importantly it will help reduce the risks associated, by replacing problematic systems with new ones that can be guaranteed to give

superior performance and compliance, hence becoming more economic in the longer term.

The business model

Once the scope of the revalidation exercise is decided, the business approach to executing it has to be determined as this will enable setting a budget, targets and milestones, i.e. a plan. We are still in the context of the first revalidation as it is the most resource demanding but also the one with the most benefit, as subsequent revalidations will be merely maintaining the new status achieved, through strictly enforcing a change control procedure. There are two main business options for performing the first and major revalidation, either to use in house staff or contract staff. We look at each briefly below (Figure 6).

In house staff

Two approaches can be taken in using in-house staff on a revalidation project. The first is to use the regular validation staff to perform this task beside their daily validation duties. Whilst the direct cost of such an approach is low compared to others, experience indicates that it is hard to establish focus and to maintain commitment. The second approach is to form an ad-hoc committee to handle the revalidation project until its completion. This does provide better focus and more commitment but still takes a long time to achieve the target.

Contract staff

Again there are two possible approaches here. The first is to employ contract staff on individual basis and manage them by a competent person from the in-house staff. This person will have to have both adequate technical abilities and more importantly excellent managerial skills, as s/he will have to manage an inhomogeneous team of individuals of different professional, industrial, educational and possibly cultural backgrounds (such as the case in the free movement of labour within the EU). This will obviously be costlier than having the in house staff perform the job, but will entail higher commitment and a defined time frame.

The second option is to contract out the revalidation job, whereby a validation consultant/contractor will handle the job altogether with only a liaison person from the owner side. In terms of direct costs, this option is normally the costliest especially if assessment of the validation status is in the remit of the contractor. In addition there are indirect costs involved in auditing and approving such contractors as part of a firm's supplier audit procedures. On the other hand however, the owner will get higher commitment with respect to time, and can stipulate penalties in the contract if milestones or time obligations are not met. Furthermore, the contractor by virtue of working on different projects for different customers brings in significant experience to the firm. The down side of employing a contractor however, is the loss of knowledge of the process once they have left. Attempts should be made to capture as much of this knowledge as possible whether in writing or in person

by the in-house staff. Unfortunately, again experience indicates wide variability in the cost and commitment of validation contractors.

The purpose of this section is not to give the best approach or to provide a one-size-fits-all solution, but rather to present the different options to choose from. The final decision will not only depend on the budget a firm is committing to this exercise, but also on the level of expertise in the firm. For example some biotechnology start-ups may lack the engineering or regulatory experience necessary to perform validation activities (for commercial production), in which case a consultant/contractor may be the only option.

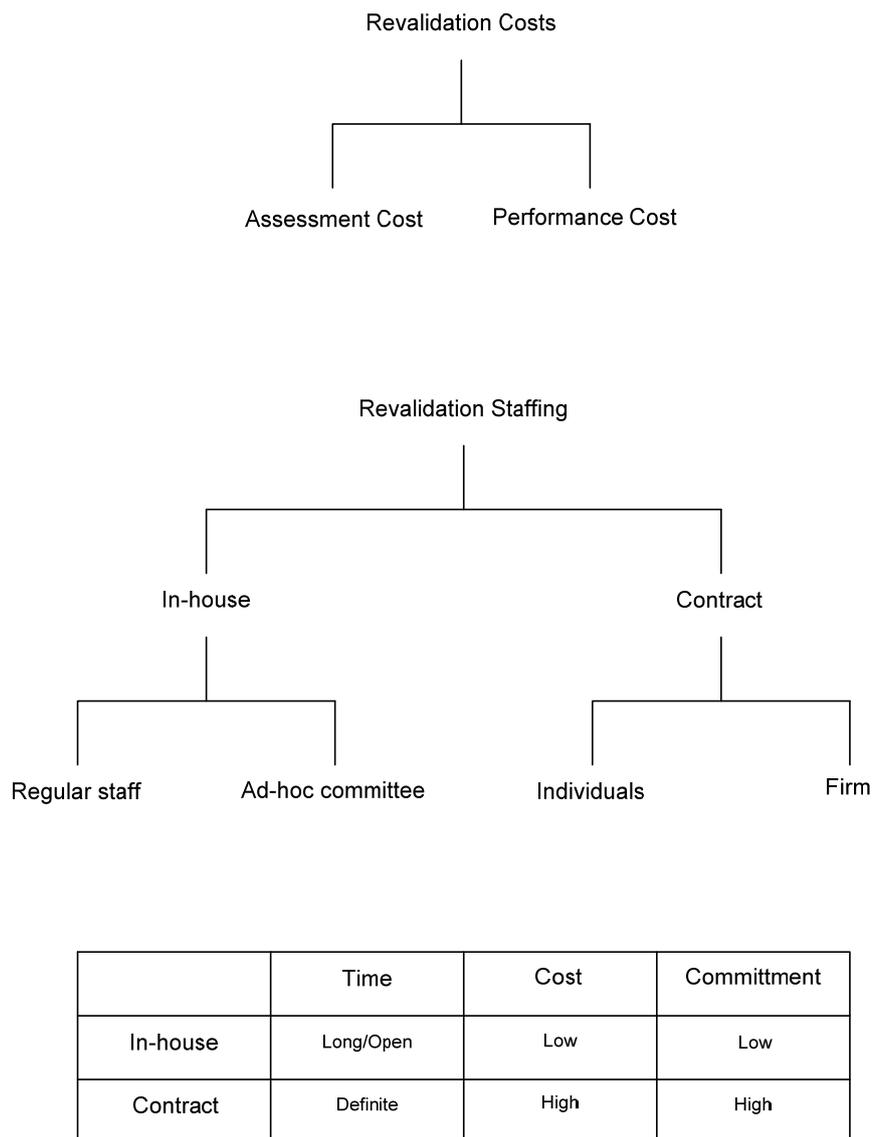


Figure 6: Business issues related to revalidation

Once the first revalidation is completed and all the product quality impacting systems have been brought into compliance, it is imperative to keep them in this state and to avoid them drifting out of it. This will necessitate regular (in any of the senses mentioned earlier) revalidation or re-evaluation of those

systems. This can be achieved by making this re-evaluation part of the regular staff tasks, or by employing staff dedicated solely to managing the re-validation and the change control processes.

In general there are several models for utilising personnel for performing the validation function in an organisation, depending on where validation responsibilities lie. For example when validation is part of process development, staff may be aligned with products or product classes. When part of engineering, they are aligned either with facilities, e.g. certain sections of a factory, or with lines and equipment. Alternatively, validation can be part of the Quality Assurance (QA) function, in which case validation personnel tend to work on different projects involving different products, facilities and equipment. Cleaning, microbiological and analytical methods validation are normally within the remit of the Quality Control laboratories.

Conclusion

In this article we presented a strategy for planning and executing revalidation of existing systems, with particular emphasis on the first revalidation. The main facets of this strategy are summarised in the accompanying figures. One key component of it is change management as it determines the need for revalidation and subsequently guarantees maintaining the acquired validated status. We believe this approach to be a pragmatic and rational one. Its main essence is to base the key decisions on the potential risk associated with the different activities, mainly risk to the patient but also risk to the business when appropriate.

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