Taming the Tyrannosaurus of validation

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Abstract

In this paper, the authors argue that the process of validating equipment in the pharmaceutical industry has become so complex and unwieldy that it may actually have become counter-productive. Such large volumes of documentation are produced that the critical test data can be lost in a welter of largely irrelevant information. It is suggested that validation needs to be rationalised into a generally-agreed format, and slimmed down to a more effective structure. The validation process could be based on the Requirement Traceability Matrix (RTM) which follows each point in the URS through to closure. The universal log-jam of document approval has to be addressed, perhaps by reducing the numbers of people required to review and approve protocols. The layout of protocols could be more standardised but above all, validation needs to take stock of what is central to the process of ensuring product quality and operator safety.

Introduction

Why has pharmaceutical validation become so very difficult? Why does it now require an army of validators, generating huge volumes of paperwork, to qualify pharmaceutical equipment? Does anyone actually read through all the mountains of documentation, and in the final analysis, are product quality and operator safety genuinely maintained by present practice? Has validation in fact become a sort of academic box-ticking exercise, designed to test the lateral thinking ability of highly-paid validators?

A huge meteorite strike wiped out the dinosaurs 66 million years ago, and paved the way for the more agile and adaptable mammals to inherit the planet. Is a meteorite on the way to hit the dinosaur that is current validation practice, to open the way for more concise, logic-based, easily-followed qualification?

In practice, the situation may not be quite so dire, but the cost of medical care is going to be squeezed by aging populations, demanding ever-more sophisticated treatment, and so the costs of pharmaceutical production will have to be reduced. Simplifying validation may be one of many routes to checking those spiralling costs. And we may even improve validation overall as a result.

Where do we start? Well, can we first agree on the sequence of documents that are required to validate a given piece of equipment? And then can we agree a reasonably standardised format for those documents? Next, can we agree a good method for keeping track of the documentation?

After that, we need to tackle the very thorny issue of who does what, and when? In our experience, projects almost invariably become bogged-down by the failure of individuals to review and approve documents in a timely fashion. Everyone, it seems, has more important things to do than sign off a validation protocol. It should not be necessary, as we have done in the past, to march around various offices on site, holding a metaphorical gun to the head of agreed approvers. This sort of issue regularly holds up the operation of new equipment that is actually functioning perfectly well, for months, if not years.

And finally, do computers and photocopiers help with the validation exercise, or do they just present a very easy way of generating yet more documentation? The specific point we are really making here is a plea to think carefully about what actually needs to be verified to ensure product quality and operator safety, and how that can be documented most simply and clearly. In our recent experience, when the FAT, SAT and IOQ protocols for a suite of half a dozen isolators runs to 4,000 pages, something must surely be wrong. We have a serious "wood for the trees" issue.

Keeping track – the traceability matrix

Setting up and then maintaining a requirement traceability matrix (RTM) is quite a chore for the validators, but it is a good way of keeping track of the documentation. In the ideal case, the RTM allows any given URS point to be tracked through the entire validation process. It is not only a useful tool for the validators, but it is also useful to the project manager, since validation work has to be programmed into the overall project time schedule. What does an RTM look like and how does it work?

Basically, The RTM is just a large matrix table. In a typical example, the columns along the top of the table list the various protocols in sequence from left to right. The first column would normally be the User Requirement Specification (URS), the second column, the Functional Design Specification (FDS), and so on through to the Performance Qualification (PQ). The rows down the left-hand side of the table list the individual points in the URS, in exactly the same order as they appear in the URS, and preferably, using the same numbering system.

The first few lines of an RTM for a hypothetical isolator are shown in Table 1.

Note first of all, how each point in the URS is fully and clearly addressed by a corresponding point in each of the subsequent validation documents. So, we can check on how any particular user requirement is handled right through the validation process.

Note secondly how some tests do not run all the way across from URS to PQ. Quite a number can be closed off at an earlier stage. For example, the URS point that requires radiused corners is not going to alter after FAT, thus once checked at FAT, this point can be closed. This is quite an important point because the RTM then shows us where any given URS point is closed off, be it at FAT, SAT or OQ.

Naturally, Microsoft "Excel" provides a good format for the RTM, but other computer programs are available. The use of colour can make the table easier to follow, and colour can be used to progress the validation with a red-amber-green (RAG) system. But don't be tempted to over-complicate the table with extra data and information – stick to the point.

Someone needs to take charge of the RTM, preferably the project validation manager. This means not only setting up the table, but also updating it steadily as the work proceeds. If the RTM is not

Table 1: The first few lines of an RTM for a hypothetical isolator

URS Point Number	URS Point	FDS	DQ	FAT	SAT	IOQ	PQ
1	The isolator body will be fabricated from 316L stainless steel	Accepted	Noted as accepted	Review materials certificate	Closed at FAT	N/A	N/A
2	The isolator body will have corner radius > 20 mm.	Standard tooling allows for 25 mm radius	Accepted	Measure corner radius	Closed at FAT	N/A	N/A
3	The isolator body will be polished to <1.0 micron Ra	Accepted	Noted as accepted	Measure Ra at a series of sites to confirm	Closed at FAT	N/A	N/A

regularly updated, it becomes progressively more difficult to bring up to date.

The sequence of documents for validation

Every project will have slightly differing validation demands, but broadly-speaking, the normal sequence of protocols laid out to document the qualification of a single piece of equipment runs as follows:

1. User Requirement Specification - URS (or User Requirement Brief - URB, or Equipment Requirement Specification – ERS)
2. Functional Design Specification – FDS
3. Design Qualification – DQ
4. Factory Acceptance Test – FAT
5. Site Acceptance Test – SAT
6. Installation Qualification – IO
7. Operational Qualification – OQ
8. Performance Qualification – PQ

There should be validation plan (VP) ahead of these protocols, but this would be project-specific, rather than equipment-specific. And most validators will produce a short-form report for the FAT, SAT, IOQ and PQ which briefly summarises the results of protocol execution.

The format of test protocols

This is an area which in our experience, seems to throw up all sorts of weird and wonderful offerings. Everyone appears to have their own pet method for recording validation tests, some logical and easy to follow, others much less so. In one case we found that the method for each test was in one document, the results were all in a completely different document, in another file, and the attachments in yet another file. Connecting the three was a major investigative exercise, not aided by lengthy reference numbers, and the absence of document names. In another case, the test results were compressed into a small table which lay within a box labelled "criteria of acceptance". How is this sort of thing allowed to happen in a technical environment?

Let's be quite clear at this stage of our argument. When the regulator or auditor asks a simple question such as "what is the tested leak rate of this isolator?" then you have 10 minutes to produce the documented evidence. Rummaging through crates of files and then leafing through hefty protocols is not going to give the impression that your validation is under control.

It seems to us that there is only one logical format for the majority of validation tests and that this logical format comes in the following sequence.

1. Title
2. Purpose
3. Method statement
4. Criterion (-a) of acceptance
5. Table of results
6. Pass / fail statement
7. Comments

If the test has actual numerical results, the criterion of acceptance can be very specific, and the test result quite clear. For example: "The isolator shall operate at 50 Pa, plus or minus 10 Pa." The test result here is a pass or a fail. Where the test results are more subjective, the criterion has to use more flexible terms such as "....deemed acceptable". For example: "The design and construction of the isolator shall meet GMP requirements." Here the test result has to be more descriptive: "The design and construction of the isolator is considered to meet GMP requirements."

Note that words such as "should" are not appropriate in test protocols. We have come across recent instances where the method statement carried wording such as "the front window seal should inflate when the isolator is switched to normal operation". Either the window seals or it does not, so the method statement is better worded "switch the isolator to normal operation and ensure that the front window seal has inflated". The results table would correspondingly state "Isolator switched to normal operation – front window seal inflates" followed by a pass / fail confirmation.

Aside from the content of the typical protocol we encounter, the headers and footers, and the design of the front page rarely seem logical to us. Quite often it is hard to tell from the front page what piece of equipment is the subject, and what is the nature of the protocol.

Can we suggest that, on the front page, the item of equipment (e.g. "Four-Glove Sterility Testing Isolator A") and the type of the protocol (e.g. "Installation and Operational Qualification Protocol") be prominent. Thereafter perhaps less prominently, we need a unique document reference number, the revision number of the protocol, correct pagination (e.g. "Page 1 of 25"), and finally the date. And on the subject of date, we really must standardise on the format DD-MMM-YYYY and no other. Again

in our recent experience, the use of the USA format caused enough confusion to almost generate a product recall.

Very often the header and footer will duplicate a lot of this information throughout the protocol, which is fine.

Finally, to end this section, can we make a heart-felt plea to use plain English in drafting protocols? Keep the wording short and concise, avoiding long sentences with multiple sub-clauses. Imagine that you are writing for someone for whom English is not their first language. This is not the place to try and demonstrate your extensive vocabulary. The word "alarm" is rather better than the word "annunciator" In short, take note of the wording on the front of a tee-shirt we saw recently. It read: "Eschew Obfuscation".

Basically, we need to minimise the number of people in the validation chain. We do not need an army of reviewers, we just need people who are competent in their subject.

How many signatures?

One aspect of test protocols that we find irritating is the frequent demand for signatures throughout any given test, with endless repetition. It is simply not necessary to sign every line of a results table. It may be desirable in some instances to initial each line, but in our view one signature is required on the pass/fail statement, and another one on the comments box, for each test or check. This is quite sufficient.

Many protocols also require that each test is signed by a reviewer, which means that the protocol must be passed to a second party for every test, adding to the delay and complexity of execution. We suggest that a review and final approval page should be placed close to the start of the protocol. The reviewer can than check through all of the tests and if satisfied with the results, they can sign off the protocol in one session.

Who does what?

Maybe the heading of this paragraph should be who doesn't do what. Or perhaps we should devote a whole paper to this topic. It's the problem that seems to gum up the works in almost every validation we have worked on. It's the problem of getting draft documents reviewed and then approved. It just seems to take forever. And it may be at the root of why validation departments are ever-expanding and always short of time. Indeed, we now have Validation Institutes, in other words a whole industry emerging from what should largely be common sense.

There is no simple solution here, a certain number of people need to look at a draft document and make comments. Then those comments need to be reviewed, the document finalised, and eventually sent out for approval. It looks very simple on the page, but in practice we find a paper-chase of comments, changes, revision, more comments, disagreements, discussion meetings, and a general resistance to move forward. The "track changes" feature of Microsoft Word probably does nothing to make the process easier, it may even contribute to the problem.

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So, what are the tasks? We suggest they are as follows:

1. Draft the protocol
2. Review the protocol
3. Collate the review comments, and revise the protocol
4. Approve the protocol

What competences, or job titles, are needed to carry out the tasks? We suggest they are likely to be as follows:

1. The equipment specialist, or technical expert
2. The validation manager, or their nominated validation engineer
3. The Quality manager or their nominated qualified person

That's it. No one else. For every extra person you add to this chain, the time to get the protocol approved will double. Add in the project manager and the microbiology manager and you do the maths. Dare we consign the dreaded Review, Approve, Consult, Inform (RACI) table, which tends to list a whole raft of personnel, to history?

So, our idealised process for the generation and approval of a validation document works like this:

1. The equipment specialist, or technical expert, drafts the protocol. This person is familiar with the type of equipment, and also with its likely validation.
2. The validation manager, or their nominated validation engineer reads the draft and makes appropriate comments.
3. The qualified person reads the draft and makes appropriate comments.
4. The equipment specialist, and only the equipment specialist, revises the draft in line with the comments from the validation engineer and the qualified person.
5. The protocol is issued to the validation manager and the quality manager for approval.

We appreciate that this suggested structure will send shock waves through most validation departments, but this is going to have to happen, sooner or later.

Drafting the URS

In many ways, the validation quagmire starts with the URS. If the URS is clear and concise, then the following validation documents fall into place fairly easily. If the URS is muddled, inconsistent and repetitive, then trouble will surely ensue. We were asked to comment on the URS for some containment isolators a year or so ago. It seemed to us that each point of the URS had been written on a scrap of paper, then all the scraps of paper had been tossed in the air, and the URS assembled at random from the resulting confetti. It was difficult to generate the subsequent IOQs for the isolators from the illogical sequence.

Think carefully about the structure of your URS. Work from the general to the specific. Group topics together: using an isolator as an example, perhaps describe the ventilation system as a topic section, including the air flow regime, the isolator pressure regime, and the filtration.

Some validation departments like to use the exact wording of each URS point in the criterion of acceptance line where that point is examined in the FAT / SAT/

IOQ. This seems to us a rather extreme approach, but it is at least made more workable if the URS has been drafted with suitable wording.

Conclusion: validation by CXS

In conclusion, we feel that pharmaceutical validation has started to get out of hand. Instead of a logical and orderly operation to ensure the quality of products and the safety of operators, it has become a self-perpetuating, rambling and over-complex industry in its own right. We need to step back, consider the logic and the science, and then move forward with what we might term "Validation-Lite".

Our suggested validation techniques are based on the CXS principle where:

C = Common
X = The expletive of your choice
S = Sense

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