EU QP: Custodian of quality or piggy in the middle?

by Hedley Rees

EU legislators are likely to respond unambiguously in answer to the above question; the EU QP is the custodian of quality in an industry where patient safety is paramount. The argument would follow that someone has to carry the can for quality, and that person must be knowledgeable in all relevant aspects, and must be certified as so. Then each and every batch intended for sale or release for further processing must have the QP's signature to prove all was well along the way. To do this, the QP has to review all relevant documentation that has been assembled… and then sign in blood.

The validity of this approach is at least questionable, and borders on lunacy. Holding a single person or function responsible for quality runs counter to all current received wisdom on how modern production systems should operate. Other sectors (such as semi-conductors) have driven their quality levels up to six sigma and beyond by placing responsibility for quality on those adding the value, principally production operators and others physically impacting the product. It is only if these players perform their tasks in a 'quality ' fashion, that defects and errors can be prevented. No amount of reviewing test results or process documentation will pick up those little errors or accidents that didn't find their way onto the paperwork – and some of them may not be so little. And if those errors lead to consequences, who is to blame in the eyes of the legislators – production for making the errors? No, it's the QP for not picking them up. So production is nicely sheltered from the responsibility for getting things right. Not that production is purposely getting it wrong, just that shouldering ultimate ownership for a task has a strange habit of concentrating the mind.

This isn't the end of it, either. Use of the quality back-stop is seriously flawed when production takes place under one roof or ownership. Shudder to think how hopeless it is in today's complex, multi-stage, multi-party Pharma supply chains that span the globe. The many different companies involved, with competing quality systems, modus operandi and business objectives, conspire to make the QP role a suicide mission; a fate no doubt contemplated, as the QP weighs the expectations of the production folk who made the latest batch, against the crushing burden of responsibility for what may lie beneath the paperwork.

Between a rock and a hard place

Are the legislators therefore asking too much of QPs? Is the QP positioned between a rock and a hard place, damned if you do and damned if you don't? Is the QP piggy in the middle? Call it what you will, the whole concept of such a role is seriously flawed.

Why is this so? Those who have read my previous two articles in GMP Review (11.3 and 11.4) will detect a common theme around the massive learning that has taken place in other sectors making and selling goods for customer markets. Pharma, however, has not yet opened its eyes to the possibilities and continues to press on with outmoded ideas about production, quality and supply chains. The role of quality oversight and the QP is certainly one of those artifacts of a bygone age and needs to be completely re-engineered

What would this entail? It would mean surfacing and remedying two underlying barriers to progress. One is down to the regulators and the other in the hands of the companies developing and selling drugs. Regulators first, looking to the Orange Guide. Under 'Key Personnel', Para 2.3, it states "The heads of Production and Quality Control must be independent from each other". There is a disturbing presupposition to this notion – production cannot be trusted to make quality products. Imagine if this rule was applied to our restaurants. The chef responsible for delivering the food to the counter, and then front of house tests it for suitability to go to table. Aside for the fact that all the food would arrive cold, the chef would be continually battling with his colleagues over the produce – and would have absolutely no understanding of how his or her product was performing for customers. Gordon Ramsey may have a few 'F' words to say about that!

Figure 1 shows a paraphrase summary of the responsibilities Quality and Production are charged with. Notice in the top half, the nature of the 'Quality = boss v Production = subordinate split of responsibilities. More worryingly, in the bottom half, both departments appear to be jointly responsible for most activities necessary to make fit-for-purpose products. If that is not a recipe for confusion and disaster, what is? It ends up with Quality taking responsibility for everything (as the boss) while production waits to be told what to do next; and the best that Quality can ever do is sift out the rejects and attempt to 'explain' to Production why they must try harder.

Barrier number 1

Then, we have Annex 16 of the Guide, Certification by a Qualified Person and Batch Release, some 12 years or so old with impending revision aimed at dealing with a changing world. As if to emphasis the spectacular degree to this misses the point, the proposed revisions place even greater emphasis on the QP 'strengthening' knowledge of each batch. In our restaurant analogy above, this is tantamount to ignoring the chef's role in the quality of food going to table, and telling front of house to just drop their rejects into the bin. There is reference in the document to the wider role of the QP, in terms

of position in the organisation, location, independence and product defects, but remarkably these are regarded as 'no go' areas and kicked into the long grass of future revisions to GMP or in the Q&A section on EMA's website – incredible!

A personal bug-bear of mine is where the introduction to the proposed revision concept paper talks about supply-chains being 'quite' complicated; followed by reference to modern control techniques, all of which place great emphasis on designing quality into the product and process, not testing it to death once it's made

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Barrier number 2

For the second barrier, we turn to companies developing and selling drugs. How did we end up with these globe spanning, aviation fuel guzzling supply chains that seem to belong to no-one? The simple answer is that drug developers (CMC teams) register supply chains with little or no application of proper supply chain management principles. Not surprising, since they were never trained in the discipline, but where are those who do understand? The rationale has always been 'why would we have people apply supply chain management thinking if we don't know we have a drug?' The simple answer is that it should be at worst cost neutral and dramatically raises the probability of drugs getting to market and staying there (ie. no shortages). (See my second paper – GMP Review 11.3).

So how would this work? The critical stage is pre-formulation, as a potential drug leaves discovery research and becomes a development candidate. It may be just a few milligrams or grams that have been made and tested to determine safety and efficacy. This is where the supply chain begins. The promise of that powder in the test tube can only be realised if the eventual supply chain produces it consistently according to the registered information, and delivers it to paying customers. So manufacture and supply chain take over the baton, yes? Well, actually no. At the pre-formulation stage, it is likely the CMC team is looking at safety testing in animals and test tubes, so construct a supply chain to achieve only that. It is surprising what you can get away with when converting some raw materials and intermediates into a batch of API, for delivery at a fixed date in the future (not dictated by changing customer demand); especially when the pressure is on from above to move into the clinic as quickly as possible. Building a sound foundation for the future is the last thing on anyone's mind, so shortcuts are often taken that could seriously impact the potential for that consistent supply to paying customers

Time is against us

The important questions are not considered. What about involving material suppliers to pick the most appropriate

PRODUCTION DEPARTMENT	QUALITY CONTROL DEPARTMENT
Produce according to documentation	Approve/reject materials
Approve and enforce dept instructions	Evaluate batch records
	Ensure testing is done
Check and sign documents before passing to QC	Approve specifications/methods/procedures
	Approve/monitor contract analysts
Check Dept maintenance etc	Check Dept maintenance etc
Ensure validations are done	Ensure validations are done
Ensure dept personnel are trained	Ensure dept personnel are trained

SHARED
Authorizing/writing procedures
Monitor/control manufacturing environment
Plant hygiene
Process validation
Training
Approval/monitoring suppliers
Approval/monitoring contract manufacturers
Storage conditions
Retention of records
Monitoring GMP compliance
Sampling

Figure 1: *Division of responsibilities between Production and Quality Control, according to Orange Guide.*

specifications? No time. Well, why don't we ask discovery research why they picked that scarce material only available from the nice broker who assures us all will be well? No time. Isn't the API rather insoluble for the intended dosage form, shouldn't we investigate? No time. Why are we making intermediates in China, Indonesia and Japan then shipping them to India for API production, when the Indian supplier could make all under one roof and quality system? No time. OK, then at least can't we try and work out why the process yields are so abysmally poor? Yes, you guessed it, time is against us. When the API CMC data is submitted to the regulators, this complex 'apparently simple' supply chain is written in stone; and the cycle repeats itself. CMC teams developing the drug product and final packaged product superimpose their level of complexity onto the API – each creating multiple stages that didn't need to be there. There we have it, a supply chain that is guaranteed to keep QPs awake at night.

There is, as readers will know, a European working party seeking to find answers to this dilemma, looking at ways to help the QP better understand all this complexity. Hopefully, it will have become clear from the foregoing, that this is a doomed mission. The problem runs deep and will not be fixed by getting a handle on the complexity. The only way forward is for industry to tackle the unnecessary complexity and regulators to find a way to make production the 'chef' of the Pharma world. Both need to change. Who knows if it will happen, but hopefully it's possible.

Not all bad news

To sound a positive note, this is not bad news for QPs and the world of quality assurance/control. In fact, it has the potential to transform the lives of those working in end-to-end Pharma supply chains. How so? I hear you ask.

Well, removal of Barrier 1 would result in the Production department being accountable for the quality of materials and products leaving a plant, with a leading role in the quality of incoming materials. Along with that would go the authority to make the necessary improvements and corrections within the overall quality system. There would be no impediment to QP's stepping into this role and many I am sure would welcome it. Those that would prefer not to take such a step, could build their careers along the path of supplier development, quality engineering or any of the other vital support systems that facilitate effective production outcomes. This would be far more interesting and rewarding work in comparison to reviewing batch documentation. The regulators should strive to understand their role in making this happen.

As for Barrier 2, this is also an area where QPs could make a huge contribution, working with drug developers to REALLY get involved in removing complexity from these supply chains discussed above. They, of all people, know when they audit a prospective supplier or contractor, whether it makes sense to have this stage in the supply chain, or whether they should challenge the wisdom of a multistage transfer that will add no value and increase complexity.

These may be difficult words for QPs to countenance. Consequently, I bounced these thoughts off Martin Lush, Senior Partner at NSF-DBA, leading providers of QP training and education services; we have had many discussions over the years on modernisation in the Pharma industry and we are both passionate about the topic. He certainly identified with the pressures that the QP has to endure and also the propensity for companies to restrict the role to one of documentation review and release. His thinking was pragmatic however, in that his belief was that it is better to exercise levels of oversight as in the EU, rather than not make the attempt, as is the case in other non-EU countries. That being so, dependence on this oversight runs the risk of diverting attention from the difficult changes that have to be made in the industry paradigm – on that we both agreed.

In conclusion, it should be said that none of the above could happen overnight, and any attempt to rush changes through without proper dialogue would be a potential disaster. But that dialogue has to take place, between regulators and industry, where all the baggage of the past is tossed aside and a new spirit of collaboration and common sense reigns in our industry.

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