Batch release testing: Get ready for new requirements

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We take the safety of our medicines for granted – and for good reason. This is one of the most heavily regulated industry sectors, with myriad checks, tests and controls at every step from earliest drug discovery to the moment a pharmacist hands over the prescribed medication.

Batch release testing is the final safety check that pharmaceutical manufacturers must perform. Before any therapeutic product is declared ready for distribution, a laboratory must thoroughly analyse samples to check that the product meets all safety and quality controls. Not a single dose from a batch will leave the manufacture until the batch is signed off, by the designated Qualified Person, for meeting all release criteria.

Batch release testing in law

The legislation for batch release testing in the EU exists at the national level, but must comply with EU Directives, namely:

- Article 51 of Directive 2001/83/EC[1] relating to medicinal products for human use, amended by several subsequent Directives
- Article 55 of Directive 2001/82/EC[2] relating to veterinary medicinal products, amended by several subsequent Directives
- Article 13.3 of Directive 2001/20/EC[3] concerning laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

These articles are supported by regulations published in the EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use[4], specifically Annex 16 regarding batch release by a Qualified Person.

A common market exists in Europe for batch release, so sign-off in any one EU Member State or members of the European Economic Area (EEA) provides authorisation for distribution in all European countries without any further testing. The EEA includes all EU countries and also Iceland, Liechtenstein and Norway. Switzerland, which is neither an EU nor EEA member, is also part of this single market.

Imported products manufactured outside of the EU must be batch tested at the point of entry prior to release authorisation.

Batch release is just part of a set of quality control measures known as the Pharmaceutical Quality System (PQS)[5], or ICH Q10. PQS details quality management and processes that will ensure pharmaceutical manufacturers and their outsourced partners comply with Good Manufacturing Practice (GMP).

The Qualified Person

Perhaps a little surprising is the role of a single, named individual in the batch release process. The "Qualified Person" (QP) is formally designated within the legislation as the person given ultimate authority to sign off a batch of pharmaceutical product for medicinal (or veterinary) use.

The concept of the QP was first established in 1975. It is a unique regulatory requirement that applies only within the European Union (EU), the EEA or other countries with mutual recognition agreements in place.

The QP may come from the pharmaceutical company, but is often an external consultant. They assess all the batch release test results alongside relevant manufacturing monitoring procedures and data (i.e. everything from spot checks and feedstock analyses to pipeline flow rates). Based on all this operational and analytical information, they decide whether a batch is acceptable for sale on the market or for use in clinical trials as an investigational medicinal product.

The QP must be satisfied that the product is fit for use, that it complies with the terms of the marketing authorisation and will not put subjects at risk due to inadequate safety, quality, efficacy or quality control.

It is a highly responsible position requiring specialist knowledge and experience of the specific chemical and manufacturing processes involved. A QP is certified through national professional bodies, although they are licensed to practise across the EU.

The EU Directives specify the minimum qualifications, but invariably QPs possess a deep, technical and 'on-the-job' knowledge of the entire production chain, from feedstock through to end product, including all the chemical engineering methodologies, quality control, monitoring and manufacturing site procedures.

Testing procedure

Although the legislation does not stipulate what tests should be performed for batch release, there are numerous generic and specific analyses that a QP will expect to see to demonstrate that the product has been made according to GMP and that it complies fully with its marketing authorisation.

The suite of tests (including specifications and details of laboratory methodologies where appropriate) is agreed between the pharmaceutical manufacturer in consultation with regulators during the application for marketing approval. This is an iterative process which involves discussion among a wide range of experts from the regulator's advisory boards, research scientists and personnel involved in the manufacturing process.

The specific tests vary widely between product types, their mechanisms of action and manufacturing processes. However, a laboratory will typically analyse the physical characteristics of batch samples (for tablets, this could be their colour, shape, solubility, etc.) along with a host of tests on the active ingredients to ensure that their concentrations (and any degradation products) are within regulatory tolerance and the manufacturer's own tolerance range (usually 2-5%). Finally, the samples will undergo microbiological and chemical scrutiny to verify the product contains no hazardous materials (for example remnants of the manufacturing process).

Laboratories running batch release testing must demonstrate that they can execute the specified tests reproducibly and follow the methodologies and processes outlined in the marketing authorisation without deviation.

Batch certification *versus* quality control

As stated in Annex 16, if all samples of a pharmaceutical product meet the batch specification, the Qualified Person may certify the batch for release signifying that the batch is in compliance with GMP and in compliance with its manufacturing authorisation. The European Medicines Agency provides additional guidelines[6] to ensure batch certificates issued in all European countries (and those with mutual recognition agreements in effect) provide consistent information.

The question of quality

All laboratories offering a batch release testing service must be certified by the relevant authority to provide this service. In the UK certification is granted by the Medicines & Healthcare Products Regulatory Agency (MHRA).

This certification demonstrates that the testing facility complies with the regulatory requirements for GMP. Certification demonstrates the facility is adequately resourced with competent personnel within suitable and sufficient facilities.

The certification process ensures that all analytical or quality control laboratories can deliver a compliant batch release testing service. But how do you choose the best provider? Does certification mean all laboratories provide an identical service?

Extracting value from batch release testing

The primary purpose of batch release testing is to confirm the conformance of the product, but manufacturers can benefit immensely if their batch testing contractor offers "value added" services that exceed immediate regulatory requirements.

Trend analyses, for example, offer additional insights on the quality and control of manufacturing processes, so sites can take all necessary action to prevent any batch from ever failing the release tests.

Many manufacturers stipulate their own more stringent tolerance ranges for batch testing. When samples meet regulatory standards, but fall outside internal tolerance levels, the testing laboratory will alert the manufacturer who will work with the testing facility to investigate in more detail. Similarly, the laboratory can identify when a particular batch or sample is "out of expectation"; although the analytical results are all within regulatory and internal tolerance thresholds, there are signs that the product may fail in the future unless action is taken.

Excellent relationships and high levels of customer service are especially important between the manufacturer and the testing facility when a rare "out of specification" event occurs. In this instance the manufacturer has a maximum of 30 days to identify the root cause of the error. Is this just a spurious laboratory result, a failure of the testing regime or is there something genuinely wrong with the product? The investigation will inform the final decision regarding the release (or destruction/re-working) of the batch.

It is under these circumstances that a customer-centric, service-oriented batch testing facility really delivers value for money. The facility can make a real contribution through its investigations. Scientific staff from the laboratory can use their knowledge of the product, manufacturing processes and testing methodologies to provide advice and additional support; they can also run additional tests and will do whatever it takes to ensure the investigation meets the 30-day deadline.

Excellence

Differentiation between quality control laboratories comes with the added value they provide. All certified labs will deliver results within the statutory timeframe, but do you want compliance or excellence? Do you want a service that generates an impersonal lab report or open dialogue with technical experts? How much support and advice do you receive when analyses fall outside of threshold values?

Top quality suppliers have a proven track record. They provide clients with value for money and a commitment to customer service and communication, deploying a vested outsourcing model.

Tepnel embraces 'lean'

Shifting to customer-centric service by design, Tepnel has adopted and introduced lean principles and practices across the business. Over the course of 18 months the company successfully increased its output, reduced turnaround times by as much as 50% and increased the efficiency of many internal processes.

This drive for efficiency and simplification allows the company to offer a customer-focused, value added "testing+" service for batch release. The company collaborates with pharmaceutical manufacturers to complete the release process as quickly as possible with enhanced feedback on product quality control and manufacturing improvement, value streaming its processes and eliminating waste.

See White Paper on Lean Principles for Analytical Laboratories[7]

Unconsciously competent

It is easy to forget that science – whether fundamental research or regular laboratory assays – is performed by people. The quality of a service comes down to the commitment of personnel to deliver the best possible service to their client.

Compare these two different work ethics: "consciously incompetent" and "unconsciously competent". Most laboratories still function at the former level. Quality control comes from staff being aware when "things go wrong" which they then seek to redress. Perhaps a technician muddles a couple of dilutions or accidently sets an incubation temperature too low. Good documentation, control experiments and verification procedures detect the errors. The analyses are redone – correctly – and the client receives reliable and accurate results. But at what cost? And what if errors go unnoticed?

However, in "unconsciously competent" facilities these mistakes never occur in the first place. With an embedded culture of data integrity and by adopting lean principles a laboratory can design workflows, processes and procedures to eliminate error. Instead of noticing mistakes, technicians learn to "fool proof" every step of an analysis.

When error is eradicated, a laboratory can offer stronger data integrity, waste elimination and faster turnaround times for less cost.

People power

So your choice of supplier for batch release testing probably comes down to your working relationship. Do you get on with the staff? Are they proactive about communication? Do they ask the right questions? Do they deliver reports and updates when they say they will? Are they organised, open, honest, reliable, professional and passionate about their service?

Look for a partner who tries to view their work from your perspective. You want them to meet your targets and fit their procedures around your business requirements, driving their service provision to meet performance outcomes not just delivery metrics. A laboratory that really understands your business as well as all the technicalities of your manufacturing processes will be able to provide advice and support on top of its core analytical service. The right choice of partner can potentially save you millions.

Update on Annex 16

Changes to Annex 16 have been published following a recent public consultation[8]. Amendments place greater responsibility on the holder of the marketing authorisation to ensure that all the requirements of the authorisation are met. For batch release testing, the holder will expect stringent quality control and monitoring procedures at the laboratory. They will likely favour laboratories which embed competence, quality and excellence within their management systems.

The new Annex 16 which comes into force on the 15th April 2016 places greater emphasis on open communication between the holder and the testing facility as the QP must assess the entire supply chain, viewed as a single defined process rather than multiple steps. Feedstocks and excipients must also be assured as manufactured to GMP principles. Batch release testing facilities must be ready to engage with numerous parties within the supply chain and open up their data for scrutiny.

As the pressure from regulators to assure patient safety increases, compliance is no longer enough. Pharmaceutical companies want to go above and beyond their minimum legal requirements; they want to be sure that extra levels of assurance are in place. A batch release testing facility must offer more than a simple, certified analytical service. As a critical component in the overall quality system, it must support open communication and strive for excellence, not just compliance.

Choose well

When you are selecting your batch release partner, what is the facility's commitment to:

- **Data integrity**
- **A vested partnership approach to achieve performance outcomes**
- **Seamless integration into your business and communication workflows**
- **Development of "unconscious competence" across the business**
- **Added value (e.g. additional support and advice)**
- **Direct communication between scientists and technical staff from both organisations**
- **Rapid, informed response to "out of tolerance" and "out of specification" results**
- **Lean principles?**

It is not too late to switch!

Once your batch release testing partner is named on the marketing authorisation, it is a cumbersome and costly administrative process to switch suppliers. So make the right choice first time!

However, if you are dissatisfied with the service you receive, do not despair. It is not too late to switch! An efficient testing laboratory that is committed to a customer-centric service based on vested outsourcing and lean principles can make a direct contribution to your outsourcing costs. Stronger data integrity and faster turnaround times can produce direct and indirect cost savings. So do the economic calculations, weigh up the short- and long-term financial gain that a new supplier could deliver versus the additional costs you will suffer from sticking with an underperforming laboratory. Switching could directly improve your bottom line and pave the way for longer-term success.

Tepnel transforms turnaround time

By adopting lean principles, Tepnel 'value streamed' a batch testing procedure for a global pharmaceutical firm. Although it could not alter the testing methodologies, by streamlining workflows and eliminating waste from the process, the laboratory cut the overall turnaround time from a target of 25 to 15 days on average. This roughly equates to a 40% reduction in elapsed time and labour from when the laboratory receives batch samples to certificate sign off.

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