Deficiencies found in Inspections and QP Responsibilities

Ciara Turley, HPRA Inspector

QP Forum, Trinity College, Dublin

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Key QP Responsibilities

• Chapter 1, 1.4 (xv) Medicinal products are not sold or supplied before a Qualified Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products.
Annex 16

1.3 There may be several sites involved in the various stages of manufacture, importation, testing and storage of a batch before it undergoes certification. Regardless of how many sites are involved, the QP performing certification of the finished product must ensure that all necessary steps have been completed under accepted pharmaceutical quality systems to assure compliance of the batch with GMP, the MA and any other legal obligations in the Member State where certification is taking place.
Annex 16

1.7 In addition, the QP has responsibility for ensuring points 1.7.1 to 1.7.21 are secured. These tasks may be delegated to appropriately trained personnel or third parties. It is recognised that the QP will need to rely on the pharmaceutical quality system and the QP should have on-going assurance that this reliance is well founded.

Common deficiencies seen in requirements 1.7.1 to 1.7.21
QP related issues found in inspections

- Certification statements
- Training
- Contract QP
- Reliance on quality systems
- Audits and technical agreements for contract manufacturing and testing
- Handling unplanned deviations
- Inconsistent approach to batch disposition
- Risk assessment
- Stability data

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Examples of deficiencies
Certification statements

With respect to QP disposition of batches the following was observed:-

• The QP certification for bulk batches included the statement that product was in compliance with the MA; stability data did not support the registered shelf life for the preservative content

• The QP certification for batches of finished packed stock did not indicate if batches had been manufactured in compliance with GMP and the MA
Certification of IMPs

With regard to the quality management of investigational medicinal products (IMPs), the following was noted:

• there were no technical agreements in place with the Sponsors
• the recertification QP statement for Product X (lot 1234) had been modified from the initial certification statement to remove reference to the Product Specification File and separately, the Product Specification File reference number,
• there was no packaging record for the packaging activity of bulk tablets (PP) into the shipped container (HDPE) that occurred at the site
• there was no stability data to support the re-certification of Product X (lot 1234) and application of a retest date of Nov 2016 (two and a half years after manufacture). The retest date was based upon testing of the bulk product (stored in PP containers) in May 2016 and addition of an additional 6 months from the testing date. The container closure system used in the clinical trial was different (HDPE).
• there was no defined procedure for the recertification of IMPs based upon appropriate and relevant stability data.
Training of QP

The Qualified Person was not deemed to be adequately trained to carry out the duties of that role at the site. The training curriculum for Qualified Person did not include the SOPs for the quality systems (e.g. deviations, change control), the support functions (e.g. calibration), computerised systems or SOPs related to the function.
Release of third party manufactured product

The management of batch release activities relating to sterile manufactured was deficient in that

• The company had not provided appropriate training relating to subcontracted sterile manufacturing process to some QPs responsible for the release of such products to the market

• No audit had been performed by the company (also the MA holder) at the contract manufacturing site of the injectable product

• There was no declaration of compliance of GMP provided with the batch of product by either the releasing site or contract manufacturing site
Release of third party manufactured product

Batch certification was deficient and commitments provided to the HPRA following the previous inspection in July 2015 had not been met in that:

• A technical/quality agreement with the contract manufacturer detailing QP responsibilities was not in place and no audit had been conducted

• An updated technical/quality agreement with the API manufacturer was not in place and an audit had not been conducted since 2013

• A risk assessment had not been conducted prior to the certification and release of further batches from the site;

• PQRs prepared by the manufacturer related to the manufacturing of the product were not available

• Requirements for management and oversight of contract manufacturers were not documented under the quality system.
Release of product without supporting stability data

Regarding stability out of specification assay and related substances results and subsequent release of product to the market:

• There was no manufacturing investigation to determine the root cause of the lower assay.

• Batches were manufactured and released to the market with a reduced shelf life of 17 month without consultation with regulatory authorities. (It is recognised that the company took immediate action to quarantine the product at the distributor.)

• There was limited data to support this shelf life as not all time points had been tested for batches on stability and negative trends had been noted at 6 months. This data was not extrapolated to determine if product would be within specification at 17 months.
Inconsistent approach to disposition of product

• In relation to deviation DR17-06, the continued processing (washing, sterilising, drying) of stoppers following on from batch B1234, was not justified, as the company failed to address the root cause of the contamination of the vials, even though the source of the contamination and the steps required to remove the contamination i.e. disassembly of pipework, was known at that time.

It was noted that batch B1222 had been rejected under deviation DR16-12 as a result of black particles present on the stoppers with the same root cause.
Lack of validation data to support release

The release disposition of batch 12334 was not considered appropriate as there was inadequate data to show that the process was successfully revalidated and could consistently produce product that met specification.

- There was inadequate data to support the rationale that the filler 1 was the cause of the failing assay and that batches produced on filler 2 would consistently meet specification as:
  - There was no manufacturing investigation completed to determine the root cause.
  - Results from blend analysis of a validation batches did not meet specification and There was no statistical analysis performed to support this outlier theory
  - There was a noticeable trend in reducing assay towards bottom of cone
  - There was no consideration of that the result could be a true reflection of the homogeneity of the batch given that the end of the filled batch failed to meet assay specification
  - There was no comparison with results from previous validation batches
QP ongoing assurance in quality system?

Several parts of the Pharmaceutical Quality System were considered deficient;

- The change control for moving of operations to the new facility was inadequate as:
  - Only brief details were recorded in the change controls. There was no risk assessment performed in advance of the move. There was no impact assessment completed. The related change control was open almost a year after completion of the move.
- The majority of corrective actions committed to be implemented by the company for deficiencies cited in the last HPRA inspection had not been completed.
- The company had received and distributed product which was outside the scope of their manufacturing authorisation.
- There was no approved technical agreement in place with the contract Qualified Person. This had been cited as a major deficiency in the previous HPRA inspection and a commitment had been given in the company response to complete the contract by May 2015.
- No recall challenge had been performed since 2014.
QP ongoing assurance in quality system?

- There was no designated Head of Quality in place at the time of inspection and the production manager had assumed the quality function until a newly appointed quality manager was in place, such that there was a lack of independence between the heads of quality and production.

- The company approach to cleaning and cross contamination control was inadequate as:
  - The company had not performed any cleaning verification or cross contamination assessment to demonstrate that the cleaning regime and methods were suitable in removing product and cleaning agent residues to a satisfactory level.
  - The company had not reviewed the cleaning history of second hand equipment before introduction into the processing area.
  - The naming convention used in the room logbooks for cleaning and line clearance was not consistent, such that it was not clear if the appropriate type of clean / clearance had been performed between batches.

- No self inspection had been performed in 2015. A similar deficiency had been cited in the last HPRA inspection and a commitment of July 2014 for corrective action had been given by the company.
Thank-you