

Change control for pharmaceutical excipients

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High profile recalls and alerts in the past few years have emphasised the importance of Supply Chain and Product Integrity in the pharmaceutical industry.

Not an easy task when you consider that a Medicines and Healthcare products Regulatory Agency (MHRA) survey in the UK identified over 1200 Excipients being used in the manufacture of pharmaceutical products currently being marketed. That figure did not include flavourings or colours. Even more of a problem when you realise that the majority of the Excipients are not sourced directly from the manufacturer but via a third party distributor or trader. In many cases there may be more than one distributor involved in the supply chain. Throw into that mix the global market with products now being sourced from many different countries, particularly India and China which adds distance and potential language and communication challenges.

Many factors affect product integrity, the pharmaceutical manufacturers cannot rely on the purchasing specification alone as an indication of product quality or as an indication of its suitability for its intended use. Some of the factors to be considered are outlined below:

Different starting materials and manufacturing processes will result in different impurity profiles even when products meet a compendia specification; however this is even more important when the product is not supplied against a recognised monograph. For sensitive products as many medicines are, small changes to the impurity profile can be significant to the process and lead to non compliance.

The nature and source of the starting materials must also be considered as this may also require additional assurances on regulatory compliances. For instance if the product is from an animal source this subjects them to the regulations on transmissible spongiform encephalopathy/bovine spongiform .The use of materials derived from genetically modified materials will similarly require assurances on regulatory compliance

The test methods used are also critical in determining if the product supplied meets the expectation of the customer. Different analytical methods may give minor but critically different results. This is extremely important when many products are released into production without full chemical analysis but on the results of a certificate of analysis.

Packaging materials is important in terms of stability, cross contamination and security. The shelf life of a product may vary depending on the packaging used. The material must be robust enough to ensure there is no risk of contamination to the product during transport and storage, but also there should be no risk of contamination from the packaging itself. Finally the packaging must also give guarantees of being tamper evident.

And of course a specification gives no indication of the GMP compliance of the manufacturer. pharmaceutical companies should only be sourcing from approved manufacturing sites, whose GMP should meet the standards required.

As part of the development and design formulation of a drug the manufacturer has to assess the impact that all of the above may have on the suitability of a material for its intended

use. Any changes to the stated criteria must also be assessed and documented and where relevant a variation to the Marketing Authorisation must be sought.

Critical to supply chain and product integrity is a robust change control procedure that allows for timely notification from suppliers of all significant changes so that pharmaceutical manufacturers can assess the impact of the change and if necessary notify the relevant Regulatory Bodies. The Regulatory Authorities acknowledge that this is a complex requirement. Change control procedures are mandatory for both FDA Regulated Companies as it is with those under the regulation of European Medicine Regulatory Authorities. Whilst many pharmaceutical companies have detailed procedures and indeed IT systems to manage change internally, these procedures and systems are limited in effectiveness if no change control agreement is in place with the Supplier or if the supplier has no change control agreement with the manufacturer. It also limited by the knowledge and understanding within the supplier's organisation of the products that are being supplied, the whole supply chain, Pharmaceutical Regulation and also why and what changes need to be communicated. Many suppliers operate the ISO 9001 management system which does not put the same emphasis on change control as that outlined in the ICH Q7a Guidelines and they may therefore not have effective procedures for communicating and assessing product changes within their own organisation.

So what should a comprehensive change control agreement include?

Changes to any of the following must be included in a supplier's chain control agreement:

- Manufacturer;
- Site of manufacture;
- Supplier;

- Supply route;
- Manufacturing process;
- Specification;
- Impurity profile;
- Raw materials or Feedstock;
- Test methods;
- Certificate of analysis;
- Packaging material;
- Labelling information.

CHANGE CONTROL AT UNIVAR

As a key supplier of excipients to the pharmaceutical industry, Univar realised that if we wished to continue being a key supplier we had to operate to the standards expected by the industry. We understood that change control was not only critical to pharmaceutical customers, but also important to safeguard Univar's liabilities and to understand our customers, products, suppliers and supply chain better.

Following a review at the start of 2008 of our then current change control procedure Univar set about putting place the rigorous change control procedures we have today which reflects the needs of the pharmaceutical industry.

Our review highlighted two key focus areas which were:

- Change control agreements with suppliers;
- Communication of change internally and externally.

However before we addressed either of those concerns we felt we had to ensure that the information on products, specifications and suppliers was up to date. We also set up a central data base to hold all this information and manage all the change control information.

We then started the process of drawing up and sending to all our suppliers of products for the pharmaceutical industry change control agreements which detailed the changes that we needed to be notified of. Many

chain control agreements in the industry simply state notification should be made of "any significant change". This is too vague, suppliers can't know what changes might or might not be significant to the customer's process or product, and therefore we asked that all changes be communicated so that the end user can assess the risk.

As expected not all suppliers will agree to sign up to this, some will only agree to parts and whilst this is an area we are still working on, it was useful information. We then knew what we could and couldn't agree to when asked to sign off change control agreements. It also allows pharmaceutical manufacturers to assess the risk associated with using particular excipients and putting the appropriate controls in place. Whilst not ideal it is better than having a misguided believe that all changes will be notified.

Ultimately though, it all hinges on communication and the information getting to the right person.

Setting up a change control mailbox for both suppliers and colleague to send details of change proved to be a quick win, especially when we linked it with a programme to raise awareness internally of the importance of change control and change management for our own products.

So, how do we finally communicate changes to our customers?

Our current ERP system in the UK and Ireland offered the solution; with the help of our IT department the system can pull details of all customers who have received a product in a designated period of time. Details of the change are entered and this will be automatically emailed or faxed to the designated customer contact. All customer contact details for change control are stored on the system. It records what was sent, to whom and when, which also gives us the necessary traceability.