Change Control at the Global Level

Organisations need a reliable process to ensure that those evaluating and managing changes to the manufacturing process address the needs of the global company – not just those of the plant immediately concerned.

The top 50 pharmaceutical companies have long lineages, often going back to the early 20th century and before. Most have grown up through a series of mergers and acquisitions that have left them with complex manufacturing and distribution structures. Recent rationalisation has, in some ways, made these structures even more complex. In the 1970s, for any given product, there would have been many local plants and distribution centres serving much more localised sales destinations; today, most have significantly rationalised their manufacturing supply chain, reducing the number of manufacturing plants and increasing their reliance on a number of strategic third-parties.

This globalisation of the supply chain can often lead to several specialist plants in different parts of the world being involved at different stages of the production process. For example, the powder (active ingredient) might be made in Singapore and then shipped to the US to be formulated into tablets. From there, it could be shipped to Ireland to be put into blister packs, before shipping of the finished product to all European markets. Some of the product may then be shipped on to Turkey, where it could be re-packaged or re-labelled at yet another plant. In some cases, third-party manufacturers or distributors may also be involved. This makes it difficult for anyone within the company to take an end-to-end view – to know exactly what went into the 50-gallon drum – and also to be aware of all the ultimate destinations of the finished product, and their respective needs.

The difficulty of pulling together information from all stages of the process makes it hard to deal with and evaluate change. It is difficult to ensure that local organisations are notified of a forthcoming change so that they seek the necessary regulatory approvals at the right time and update the relevant documentation. It is also difficult to be sure that a change that makes sense in the context of an individual plant will still make sense when its global repercussions are considered.

This article looks at how even a relatively minor change to a manufacturing process at the local level can have implications throughout a company’s global operations, and puts forward a framework to manage change effectively in today’s complicated and highly regulated environment.

ENSURING REGULATORY COMPLIANCE

The complexity of the manufacturing and distribution process, coupled with the remoteness of many markets from manufacturing sites, poses problems when it comes to ensuring regulatory compliance. To sell a given product in a given country, the company must secure regulatory approval for it, and every time a change to the manufacturing process is made, that approval may well need to be updated. This means that each country needs to maintain an up-to-date marketing authorisation dossier for the product, and that marketing authorisation may be significantly different from others for the same product manufactured at the same plant.

The content of the marketing authorisation dossier varies from country to country depending on the regulatory environment. The content generally includes:

- Clinical information – proving that the product does what it is supposed to do
- Manufacturing information – details of how the product is made
- Quality control information – the acceptable parameters for the product
- Supply chain information – details of the temperatures at which it has to be kept and the containers in which it has to be stored

The information contained in the marketing authorisation dossier is often an extract or summary of many other documents. For example, the manufacturing section often summarises the Chemistry Manufacturing and Control (CMC) documentation. With the same information held in many places – for example, in the manufacturing dossier and multiple marketing authorisation dossiers – it is difficult and labour-intensive to make sure that a process change reaches all the documents that should reflect it, and that it triggers all of the necessary applications for regulatory approval. If a piece of machinery in the manufacturing plant breaks
down, it might be desirable to replace it with a faster one, but this new one may need to be operated at a higher temperature. This change to the manufacturing process may necessitate re-approval in all the countries where the product is sold and updating all the marketing dossiers. These approvals can vary from end-of-year notification of change in one market to two years prior approval in another, and this difference between markets adds another layer of complexity to global change control.

This is a relatively recent problem. When the manufacturing process took place in one plant for each country or region, keeping marketing documentation up to date would have been relatively straightforward: there would have been one set of documentation per country and the sets would have been fairly independent of one another. With a single global manufacturing process having to satisfy the regulatory requirements of many countries, change can be extremely difficult to manage. Yet it’s vital that, if a change happens in a factory in Singapore, all the affected marketing organisations – from Brazil to Europe and Australia to the US – hear about it in sufficient time to seek the necessary approvals and update the relevant documentation.

GLOBAL IMPLICATIONS OF CHANGE

With a single global manufacturing process having to satisfy the regulatory requirements of many countries, change can be extremely difficult to manage. The rise of a complex global manufacturing and distribution process means that it is very hard to make fully informed decisions about whether to go ahead with a proposed change. A product might be made in one plant and then sold in 70 countries. A plant manager might identify, for example, that if a machine were to run faster it would save 100,000 Euros; what that manager may not realise, however, is that the change could necessitate resubmitting the product for regulatory approval in 50 countries – a process that could cost hundreds of thousands of Euros, so that what might be a gain locally would in fact be a loss for the company overall. That loss is distributed across the marketing affiliates, and demonstrates that introducing Global Change Control requires not just a process or system, but a fundamental review of the way that those who work within the supply chain are rewarded.

Consider the following example: a company has a global product generating $2 billion in annual sales. If it fails a safety test anywhere in the world the manufacturer is bound to inform all the regulatory authorities of the failure (even if their country does not actually require the test). The introduction of a new safety test in a relatively small market (due, say, to a change in regulation) might put the global sales of the product at risk, not just local sales in the country where the new test is being mandated. The decision to include the new test and its documentation in the CMC is therefore a global strategic decision, not a simple change in local regulation. Global visibility and global decision-making are now critical. Inevitably, over time, many different aspects of the manufacturing and distribution process will change. Large pharmaceutical companies may handle many
thousands of change requests each year for the CMC sections of the dossier; artwork and labelling changes are generally even more frequent.

A GLOBAL CHANGE CONTROL FRAMEWORK

So how can companies effectively manage change in today’s complicated – and highly regulated – environment? The solution is to put in place a global change control framework. Our experience in implementing such a framework suggests that there are four main elements to consider in implementing such processes: accountability, organisation, processes and technology.

Accountability

From its initiation, each change needs to have a clearly identified sponsor, accountable for the robust evaluation of the change. 'Robust' implies, amongst other things, that changes must be evaluated in terms of their impact across the entire company and not just locally. The sponsor needs to consult all stakeholders (of whom there may be a significant number). To facilitate consultation, these stakeholders should form a Change Review Committee containing representatives of all major stakeholder groups, which are accountable for reviewing each change from the perspective of their function. The committee should be constituted so as to ensure that technical and financial issues are considered along with those relating to quality control, timing or project management. It must evaluate the global impact of a change, identifying, for example, whether the expense of obtaining regulatory approval in every country would outweigh the local benefit for the plant, as in the situation discussed above. The sponsor should then consolidate the various opinions into an overall recommendation. Not all products are marketed globally and so a hierarchy of local, regional and global committees and sponsors may best fit the needs of the organisation. There is usually no need to recruit or appoint new people to be responsible for reviewing changes. There is often an existing global regulatory affairs group and a group responsible for conformance and quality; some combination of these can be enlisted to form the Change Review Committee.

Organisation

From a regulatory perspective, it is essential that the Change Review Committee – and the sponsor for each change – are independent of plant management, and thus will not succumb to pressure to view change purely from a plant-oriented point of view. Since plant management’s main objective is to get product out of the door faster and at lower cost, they are likely to be biased in favour of changes that reduce the cost or duration of the manufacturing process. Independence makes business sense too. An independent change management group will look right across the organisation to make better informed decisions: it will rightly reject a change that is acceptable in terms of manufacturing bulk product and tablets, but then falls apart from a packaging perspective – for example, because of the tablet’s humidity constraints. Instituting this type of change control mechanism will also require a cultural and organisational transformation of the business as a whole. The purpose of change control must be communicated to staff so that they see the new framework not as a costly tax on the business, but as a key success factor for ensuring product supply. For the company as a whole, adopting the framework does not necessarily represent additional work so much as a change of mindset. It simply means acquiring an understanding of the type of impact that a change could have elsewhere in the business.

Process

A typical top-50 company will already have multiple change control systems in place. The challenge is to replace them with a single, scalable process that accommodates every dimension of change control, and that is used in a consistent way by everyone in the company. The aim should be to ensure that the outcomes of a change-related action are recorded, not every interaction and deliberation that precedes that outcome.
There is no doubt that, given the complexity of the modern pharmaceutical business, replacing all change control processes in one go carries too high a risk; however, setting out a vision, defining the process models and integrating the processes and systems over time is possible. There are also several distinct flavours of change control within an organisation, and the differences between these are real; artwork and labelling change control is different from manufacturing change control in a plant or marketing authorisation change control in the affiliate. These differences must be recognised and care taken around their change.

Communication is crucial to acceptance: everyone believes that they already know all about change control. Rather than just accepting the new process, all relevant staff should be equipped to carry it out themselves since directing every action from the centre would constitute a bottleneck.

**Technology**

The objective should be to automate the process of evaluating and communicating change sufficiently to ensure that decisions are taken in a timely way, and that they trigger all the necessary actions and updates. The type of system that is required can be built from standard elements like workflow and document management. Complex or highly customised systems are best avoided as they are expensive and can constrain flexibility. The system should ensure that the change sponsor and change control committee members are reminded of their accountability for decision-making and for maintaining information; the key is to present the right person with the right task or decision at the right moment. The system should also be capable of assembling information from different parts of the company: the manager who needs to decide whether to run a machine faster needs to know the cost and time-scale for approval in each country – information which is undoubtedly already known in that country’s regulatory operation and can be collected from it. The consistency of documentation also needs to be managed to ensure that a change to manufacturing documentation reliably updates, for example, all the marketing dossiers. Since one company may have many millions of pages of documentation to maintain, and may need to deal with several thousand change requests per annum, automation is the only way to guarantee accuracy. While most large pharmaceutical companies have document management in place, they need to review it regularly to ensure that it meets requirements. With the right systems in place, it also becomes possible to report information on the change process itself – for example, to notify the FDA about how long a change request has remained open, first batch release, first use of a labelling component in a production run, and so on.

The change control system, like the process it embodies, must scale and adapt to different situations. For those products that are purely local, change control should follow the same basic process but will not involve the same level of consultation as for a global product. In these cases, it may make sense to decentralise change control, and the system should be able to refer decisions to the correct people. But sharing the same framework for changes at all levels ensures that best practice is always followed.

**THE BENEFITS TO BE REAPED**

By focusing on these four elements of accountability, organisation, process and technology, companies can put in place a robust change control framework that makes it possible to evaluate every proposed change from a global perspective and to ensure that changes are effectively communicated to those who need to know, including all local marketing operations and the regulators with whom they have to deal. We have found that it is possible to achieve a simple and universally understood process with clearly defined accountabilities. A single, scalable process can be used in a variety of situations: plant to plant, plant to affiliate and affiliate to affiliate. Finally, care must be taken to see this not just as a technology or business process engineering exercise. Global change control is a truly complex problem that touches everything from the extended supply chain to product marketing and new product introduction; it will require collaboration from across the business over a significant period of time. It is possible to put change control processes in place that meet the global needs of the business – but it is not easy! As well as better informed decision-making and improved regulatory compliance, benefits include better alignment with the supply chain and a reduction in potential disruptions to it. By avoiding noncompliance and under-informed decisions, a watertight change control framework can avoid substantial future costs.