



Investing in patient safety

The complex world of labeling in the Life Sciences industry

Transforming organizational capabilities series

Life Sciences companies are held to very high standards by Healthcare Authorities and their end customers to guarantee the safety of the drugs they manufacture. An important process to ensure patient safety is the timely update of label information along with the medicines they sell. KPMG member firms' experience working with professionals in this critical process has revealed issues with misalignment between teams that may warrant the need for operational and organizational transformation in both the medium and long-term. With rapid technological and regulatory changes globally, this presents an opportunity for the regulatory affairs and manufacturing teams of pharmaceutical companies, particularly when patient safety is on the line.

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Patient safety is paramount

Pharmaceutical companies must demonstrate to Healthcare Authorities and healthcare providers that the medication they sell is safe for patient use.

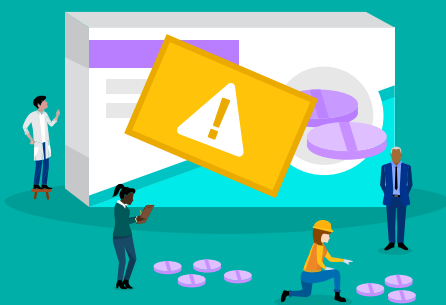
A key part of a pharmaceutical company's license to operate is their ability to satisfy stringent demands from the relevant Healthcare Authority (HA) and quality inspectors. One of these is the updating of the safety label information in medical boxes to meet additional new information regarding the safety profile of in-market therapies.

An ongoing challenge across many pharmaceutical companies is the continued disconnect between label change process objectives and operational requirements of regulatory and manufacturing functions, particularly for 'standard' label changes as opposed to 'urgent'. This misalignment across the functions has the potential for significant negative consequences, first and foremost for patient safety but also for the financial impact and reputational damage it may cause directly to the company.

About this paper

In this paper we present a new qualitative exploratory survey setting out some of the challenges KPMG professionals have observed related to this disconnect on standard safety label changes, as well as a view of potential solutions to ameliorate the situation for both patients and pharmaceutical companies.

KPMG professionals interviewed senior regulatory and manufacturing labeling professionals in 10 global companies between February and April 2018, to understand how they defined, reported and tracked medical label implementation. The companies were all global pharmaceutical companies ranging from US\$10-80 billion in annual revenue. In this paper, we look at the results of that exploratory survey and what this may mean for the future of medical labeling and ultimately, patient safety.



Why is the label important?

While patients will generally seek advice from a healthcare professional, the label contains critical information about the dosage, effects, and side-effects of a drug.

The label also gives specific warnings, for example, about the expiry date and storage requirements. There are reported cases of fatalities resulting from patients keeping drugs at home beyond the expiry date and children ingesting drugs that have been improperly stored.

Pharmaceutical companies spend a substantial amount constantly updating these labels, together with information on the drug package or container and package inserts.

It is critical that this update is done in a timely and efficient manner as it is directly correlated to patient safety and affects a pharmaceutical company's reputation.

A label update is required for an identified development in the effects of the drug, like newly discovered side effects, that could potentially compromise patient safety. This development triggers the complex Safety Labeling Change (SLC) process that involves expert teams from the Regulatory Affairs team and manufacturing function to ensure the timely delivery of this change.

Figure 1: Summary of the SLC process



In all companies, an SLC is either categorized as 'urgent' or 'standard'. Urgent SLCs have serious or potentially fatal implications for patient safety and are always prioritized by the company with no delay. Standard SLCs are less serious but affect patient safety.

Figure 2 describes both types of SLCs in detail. Urgent SLCs are extremely rare and the focus of this paper will be the standard SLC process.

Figure 2: Types of SLCs

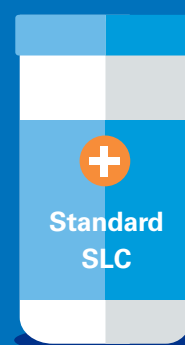


The 'urgent' SLC is triggered when a significant issue is identified with the medicine that could lead to an adverse effect on the patient including loss of life.

This type of label change is extremely rare. All pharmaceutical companies prioritize this above all activity to implement it very quickly.

This also leads to total product recall from the market to update with new labels.

This paper will not look at these SLCs as they are implemented as a priority without any delay or misalignment.



The 'standard' SLC is triggered when an issue is identified with the medicine that would not necessarily lead to patient fatality, but could affect patient safety (e.g. minor side effects, dosage).

This type of SLC is more frequent and part of the routine activity of regulatory and manufacturing teams.

In these cases, product recall is not required, but HAs require pharmaceutical companies to demonstrate timely implementation of these label changes.

This paper will focus on this type of SLC.

Challenges with the current SLC process

This exploratory survey highlighted some challenges with timelines, reporting and financial risk, impacting the companies interviewed.

KPMG professionals conducted in-depth interviews with senior regulatory affairs, quality assurance and manufacturing professionals. The objective of the discussion was to understand their SLC processes and their current challenges and pain points. We asked a series of targeted questions including:

- ▶ **What triggers a standard SLC process?**
- ▶ **At what point is the process complete/implemented and how long does it take?**
- ▶ **What milestones are tracked internally and for inspections?**
- ▶ **How is the regular supply chain cycle affected by a standard SLC?**

In this section we explore the key challenges highlighted.



Misalignment of process and timelines

Definition of implementation

Companies view implementation of the standard SLC differently. This difference is not dependent on the size of the company but on how the company perceives patient safety from a process milestone standpoint. In some cases, this difference of perception exists between the regulatory and manufacturing teams within the company.

We found that the range of what is comprised within the definition of implementation varies from just updating the label template (i.e. artwork) in the system to also including when an updated label pack is released for distribution in the market. Other definitions include ensuring that manufacturing ceases production of the old label, or when the first batch with the updated label is shipped from the manufacturing unit.

We are very risk averse and would ideally like to track and define implementation all the way to market release. However, our complex supply chain and misaligned IT systems makes visibility very difficult.

– Senior director, Regulatory Affairs,
US pharmaceutical company

Because we don't really have control on what happens to our product after it enters distribution in the market, we define implementation as when our manufacturing unit stops producing products with the outdated label.

– Senior director, Manufacturing,
European pharmaceutical company

Timelines

All of the companies KPMG professionals spoke with had defined timelines for key milestones leading up to the point of implementation. Following this, once the process is complete, companies have indicated that they do track the process if possible, but do not necessarily report it to HAs during an inspection.

HA inspectors often request pharmaceutical companies to provide timelines for implementation. For instance, the Medical and Healthcare products Regulatory Agency (MHRA) in the UK requires that SLCs are implemented six months after HA approval. Our interviews have revealed that this requirement is interpreted by each company based on how they can demonstrate and define implementation.

For instance, if a company says that a standard SLC is implemented when their manufacturing unit discontinues production of the old label, they can demonstrate that this is done in the requisite six months. On the other hand, if another company says that they track and report an SLC as being implemented when a new label batch is released to market, they would impose the same six month timeline. This leads to additional steps being completed in less time leading to a strain on activities and capacity constraints in these companies.

We don't always impose timelines as we have the ability to check real time approval of artwork and manufacturing. However, this means deprioritization and long timelines!

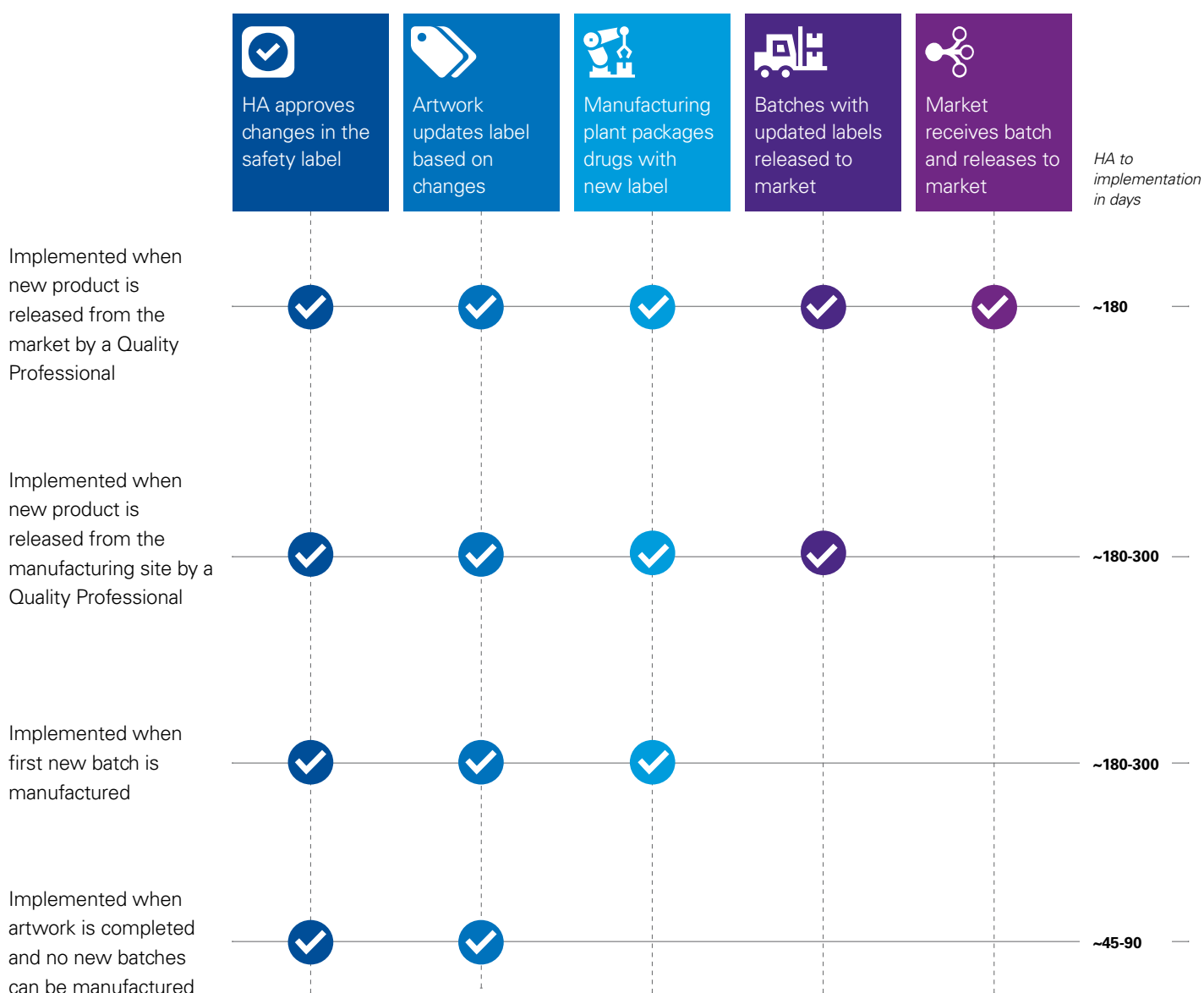
– Manager, Regulatory Affairs,
European pharmaceutical company

We have prescribed timelines for each step to meet our 90 days target, but that's not how the system tracks it.

– Senior director, Labeling
US pharmaceutical company



Figure 3: Standard SLC process variation and timelines for implementation identified from interviews





Financial risk

Since all products are manufactured based on forecast demand in a market, an SLC disrupts this manufacturing cycle by superimposing the SLC implementation timeline leading to an out-of-cycle manufacture. This forced production has been acknowledged as challenging by all companies we spoke to in this survey.

Once the new batch is manufactured and sent to market, the excess inventory already in the market is either destroyed immediately or allowed to be used for a period of time agreed by the company and market. This leads to a substantial cost in write-offs to the company.

Companies we spoke to have indicated that they have tried to manage this cost by planning in advance to alter the normal supply order when an SLC is expected to occur. This is not, however, straightforward due to limitations on the minimum order quantity that manufacturing can produce. In addition, with delivery of less than forecast orders, there is a significant risk of stock-outs in the market.

In the past we tended to burn huge quantities of old product due to bad inventory management. This is less now but still present.

– Manufacturing head,
US pharmaceutical company

We can sometimes have issues with outdated labels on the shelf in some markets and this is a major patient safety risk factor.

– Senior director, Labeling,
US pharmaceutical company



Challenges with tracking and reporting the process

The majority of companies we spoke to suggested that individual teams meet target timelines in most cases and that delays are generally due to capacity issues. However, the single most significant issue facing companies is the difference in internal IT systems used by the different teams in this process. This is further compounded by the fact that many companies use products outsourced for manufacture to other companies who also have different IT systems. This interface mismatch means that information and therefore compliance is not always recorded accurately for audit situations despite actual work having been completed on the ground.

The result is that companies spend a significant amount on IT transformation projects (such as Agile software development) or to train overloaded employees to use systems they are not familiar with.

We don't have the ability to track when a new label enters the market and have little influence on any risk after it leaves our manufacturing unit.

– Senior director, Supply Chain,
European pharmaceutical company

How much influence do pharmaceutical companies have on patient safety in the case of a standard SLC?

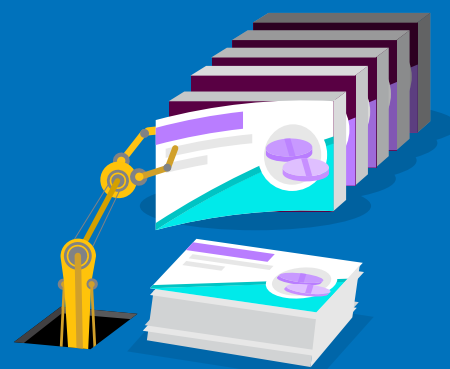
KPMG member firm professionals' experience working with SLC professionals has revealed a debate that exists about the actual capability of a pharmaceutical company to ensure patient safety.

Due to the multiple supply chain arrangements and distribution networks, it is generally accepted by labeling professionals in Life Sciences companies, that the physical package is no longer in the possession or purview of the company after a certain point. This means that any changes to labels past this point cannot be implemented to those packages, as they have already been distributed. It is important to point out that this is only true for standard SLCs. In the case of urgent SLCs, companies would do a total product recall. However, as outlined previously, urgent SLCs are rare.

But at what point should the company say it has done its part to ensure the safety of patients?

- Is it when the company can demonstrate that it does not produce packs with the old label anymore and therefore not worry about those that are out for production or shipped? While this shows that the company has discontinued production packs with the old label, it doesn't guarantee a timeframe by which the new label will reach a patient in a market.
- Or is it when a market has effectively ceased distributing packs at the country level after a certain time? This sets a timeline for this change to reach the patient, but is associated with significant destruction of stock for replacement and potential stock outs in the market while they wait for the new label to be delivered. Also, product recall is not a viable option as the company has little control over the product once it leaves its warehouse or facility.

This debate is what leads to defining the milestones that need to be tracked and reported to show that the company is doing all it can to ensure patient safety.



What are the options to improve the current process?

Life Sciences companies have a number of process optimization and transformation opportunities with varying levels of technology and time investment.

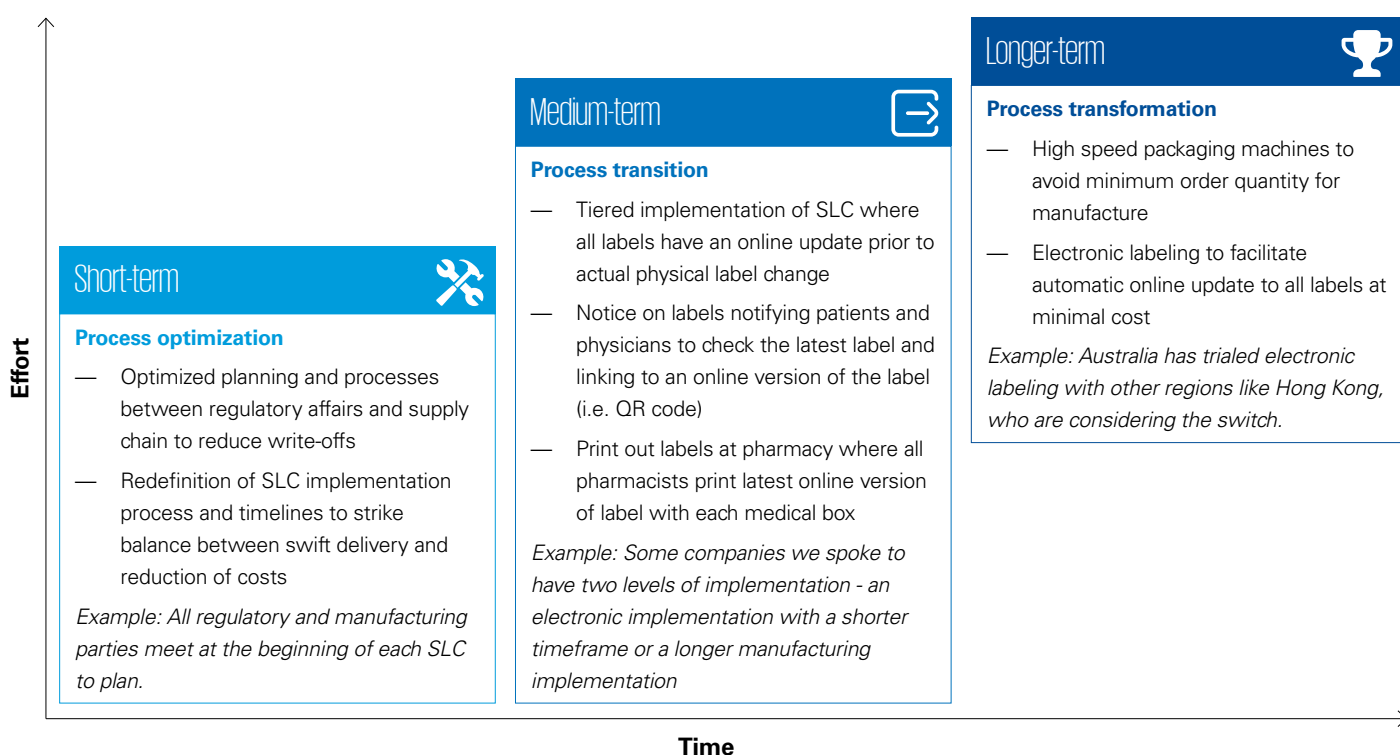
Based on our survey, KPMG professionals expect the future of SLC to follow a transition whereby pharmaceutical companies will optimize their current process in the short term whilst in the longer-term redefine it dramatically to strike the balance between speedy delivery of updated labels to the patient and minimizing costs in product scrapping.

In the medium-term, companies are likely to adopt transitional processes that will facilitate the longer-term goal, which is likely to be paperless electronic labeling where updates will be more straightforward.

One of the medium-term steps could be putting a warning or educational insert on the front cover of all boxes reminding consumers to check online for the latest up-to-date information. In the longer-term, electronic inserts might be able to be auto-updated at minimal cost to the company with no consumer action, especially with the penetration of miniature WiFi / cellular receivers.

In terms of internal company processes, there could be a review of the way in which the severity of SLCs is categorized, with lessons from other industries (i.e. tires, car batteries, food and drink recalls) to prioritize processes.

Figure 4: Expected evolution of SLC process



Are companies prepared for change?

Achieving large scale transformation to ensure patient safety requires all teams to reach a unified pragmatic view and assemble a project team with the right skills to implement change quickly and effectively.

Our exploratory survey has revealed that all the companies KPMG professionals spoke to are trying to answer three critical questions related to SLC:

1

How to guarantee the timely and speedy delivery of the updated label to the patient?

2

How to do this taking into account economic considerations?

3

How to do this without creating a huge disruption to the supply chain?

Whilst these questions remained unanswered, the industry is moving towards a pragmatic viable compromise for the status quo and making plans to shape and define the future of this vital process.

We are aware that a number of companies are undergoing large scale transformations that are expected to resolve some of these issues. One of these transitional processes is the harmonization of different IT systems. Most companies are currently transforming their Regulatory Information Management (RIM) systems to digitize and harmonize archived regulatory records to meet standards required by HAs such as Identification of medicinal products (IDMP) and electronic common technical document (eCTD) requirements.

KPMG member firms' experience has shown that these transformations require large cross-functional teams who need to manage their day-to-day functions in addition to running their transformation project. These also require post-transition change management and adequate training in skills and systems. Communication of the transition to a large group of professionals also presents a significant challenge as a mis-timed or mis-worded change announcement could lead to widespread uncertainty and anxiety about the future structure and associated redundancies or changing responsibilities.

Irrespective of whether pharmaceutical companies have the right capabilities and appetite to execute a large-scale transformation either internally or with external support, the time to make a transformation is imminent, especially when patient safety is on the line.

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Designed by **CREATE.** | CRT102187 | October 2018