Packaging Cold Chain Program Improvement

Laura Cardona Colón
Engineering Management
Hector J. Cruzado, PhD, PE
Graduate School
Polytechnic University of Puerto Rico

Abstract *— With the growing trend of biologic medicines coming to the market, a packaging engineering group needed to create an internal cold chain process to meet market demand in this area of cold shipments; although there is a process in place from a compliance quality perspective, there wasn't one from the packing side. The lack of the process in packaging resulted in gaps in the projects from one project to the next and, in some cases, some rework was required. To address these issues, the project team met and defined roles and responsibilities, determined process steps using best practices and research found and, most importantly, established the requirements needed for each project moving forward. A metric was also created to measure the effectiveness of the new process and ensure measureable improvement. A pilot is being conducted to measure the rework metric and confirm improvements are found.*

Key Terms *— Biologic medicines, pharmaceuticals, sustainability, temperature control packaging.*

INTRODUCTION

In recent years there has been a shift in the pharma industry into more of a bio-pharmaceutical industry; more and more medicines are becoming complex biological molecules that require more than just a bottle or blister for packaging. As more vials and medical devices roll out into the market, this adds complexity to the Packaging Engineering groups in each company responsible for developing packaging solutions; as part of their role, they are also tasked with making sure the product is packaged in a shipper box that keeps the correct temperature. In previous years, since most products were pills in bottles or blisters and these pills had great stability at room temperatures, packaging engineers didn't have much complicated cold chain packages. Nowadays a shift has been observed to medicines that require refrigerator or freezer storage and packaging shipping solutions.

Cold chain is defined as the process of designing shipping containers that keep products at a specified temperature range during storage and shipment. This is not a new field of work, however in recent years it has seen a significant increase in importance, particularly as more and more biologic medicines reach the market. Currently, as this field develops, some bio-pharmaceutical companies don't have internal packaging group process in place for performing cold chain projects and gaps can be observed from project to project. In route to address the gap, the quality group cold chain guide will ensure compliance as the new process was developed and align to create a packaging process that allows the team to reach the project objective of reducing rework caused by missing requirements.

The path taken will started with defining the packaging engineering role within the cold chain arena of the company. Once that was complete the next step was to identify all the requirements the engineers need to know in order to create a compliant shipper which then was followed by the creation of a process and its documentation for all to follow. A metric was created which shows how well the process was written by capturing rework data; the process was then executed and data was collected and analyzed for the metric in place; lastly results are shown alongside conclusions made.

LITERATURE REVIEW ON COLD CHAIN

Major factors influencing cold chain

There are four factors that have influenced the increase for cold chain and why companies are looking for innovations in this field. These are: the factor of unprecedented growth in the biologics drug development and commercialization which has caused a shift in cold chain; regulations have evolved to include biologics drug oversight and thus have become more intricate with the complexity added making compliance that much harder; the risk that is associated to these new drugs being developed as they have strict temperature ranges; and cost pressures have increased as the drug market switches from high volume to low volume drugs [1].

Steps to properly execute cold chain projects

The key steps to be followed in cold chain projects are: project description, project scope, deliverables, schedule, product description, transit medium, duration required, threshold temperature, ambient temperature ranges, product stability, logging and container type [2]. There has to be very good dialogue between the product team and packaging engineer in order to have a good final design; the process could be improved by several iterations [2]. Qualification is a big component in the process, and the documentation should include all testing data, results, parameters, and approval signatures [2].

Best Practices

Five best practices companies can employ in order to have a good cold chain program: total cost strategy, specialized and compliant network, globally consistent processes, risk-appropriate packaging, and technology & big data; ensuring companies have aligned global processes that are unfailing will guarantee the company has a "one mind" approach to their packaging solutions [3]. The risk level agreed should be reflected in the packaging design; in global companies, risk should be assessed across the board in a way that all involved parties are satisfied with the risk levels agreed to and as they have aligned, any packaging solutions developed would be able to be implemented anywhere in the world [3]. More than half of the world's bestselling drugs will require cold-chain protection by 2016 and as more and more drugs come out that require cold chain therefore sustainability is something all should incorporate more [4].

Cold chain outlook

The term cold chain is slowly being transitioned out as the term "temperature sensitive" has become more applicable, regulations are changing and cold chain is becoming part of the discussion at the filing level when a product is new [5]. In the future, it could be forecasted that technology could enable cold chain/temperature sensitive product packaging in better ways with the advent of phase changing materials (PCMs) and all the new capabilities they bring to cold chain packaging; and also end users will start to provide inputs to the cold chain process as they prefer reusable solutions [5].

ANALYSIS OF RESEARCH

Influencing factors of Cold Chain

Taking a look at the research available, the growing trend of biologic medicines is seen as unparalleled which has caused a major focus on cold chain like never before, as most if not all of them need to be kept in specific temperatures which makes cold chain management more convoluted than in previous years with simple pill drugs in the market. Tied to the growth are the rise of intricate regulations that are every year more and more specific and detailed adding complexity to compliance and with the added complexity comes risk since these medicines are more risky to store and ship given their behaviors to different temperature ranges; which means their stability is heavily dependent on keeping to certain temperatures. All this however must be met with wise financial management as there are external

forces pushing costs down as bio-pharmaceuticals transition from high volume "pill" production to low volume biologics.

Step by Step Process and Best Practices

There are many ways companies could go about in developing and structuring their cold supply chain strategy and processes. Looking at research there are twelve steps to follow for successful project completion as mentioned in the literature review. Two big topics emerge from these steps: communication and qualification. There has to be good dialogue between the teams and packaging engineer in order to have a good final design and smooth design qualification. The design process could be improved by several iterations and this is enhanced do to good communication making every iteration more value adding. Qualification is mandated by regulations, and the more robust is the shipper design the easier it will be to qualify.

Incorporating best practices into the process, for the purpose of this paper special focus is given to three of the six practices found: having a global approach, ensuring risk is appropriate for the packaging and sustainability. From this research, it is extracted that ensuring companies have aligned global processes that are unfailing will guarantee the company has a "one mind" approach to their packaging solutions for cold chain. Furthermore, in global companies, risk should be assessed across the board in a way that all involved parties, no matter where in the world operations are being conducted, are satisfied with the risk levels agreed to. Lastly, sustainability is a growing trend therefore eco-friendly solutions in packaging cold chain would be necessary to reduce the waste caused by the extra special packaging needed to keep cold chain packages in the correct temperature range.

Future Landscape of Cold Chain

Since the term cold chain is slowly being transitioned out and the term temperature sensitive transitions in [5], it's not enough to monitor products that require cold chain but also now products that require shipments to adhere to room temperatures which are typically considered 15-25 degrees Celsius. The future of cold chain seems to be now temperature control as any drug might require temperature adherence to any certain range, even frozen; this could potentially add many more products in the cold chain arena of the company which could increase work in this area a lot. Along with this is the case that more regulators are asking for cold chain documentation at the filing point of a new drug as their knowledge in the subject becomes better they are asking tough questions to the engineers.

RESULTS

Comprehensive Cold Chain Program

As part of the results of this project, the roles and responsibilities for each group were identified and are shown in Table 1.

Table 1
Roles and Responsibilities

Item	Group Responsible
Passive Shippers – US	Packaging Group
Passive Shippers – Ex-US	Quality Supply Chain
Active Shippers – Global	Supply Chain & Distribution
Temperature Monitors - Global	Supply Chain & Distribution

The resulting requirements found to be needed for cold chain projects are now established and documented. Figure 1 shows the identified requirements needed for the project to be successful in the real world application and globally. It's important to note that the last section in Figure 1, Other Details, contains some information required internally for a better project experience and is not requirements found in research; simply information that engineers have found helps in ensuring right first time approach.

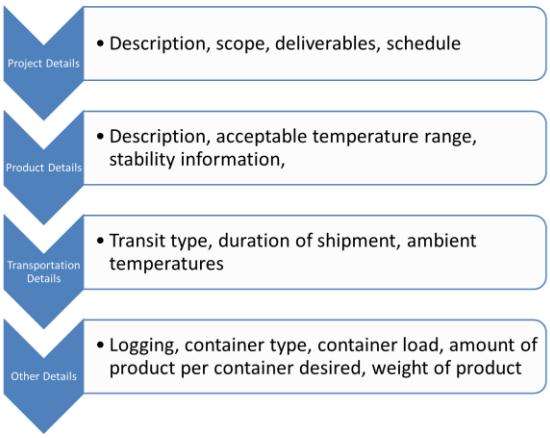

Figure 1
Information Required for Cold Chain Projects

As for the structurer for the cold chain projects and steps to follow for successful implementation, the process was established as per research found and incorporating some best practices while also taking into account suggested steps from internal team who have executed cold chain projects; the steps can be found in Table 2.

Table 2
Process Steps

#	Description
1	Obtain project information as described in Table 1.
2	Establish project team and define roles per person
3	Agree on defined project description, scope, deliverables, and schedule
4	Produce draft design and verify if vendor pre-qualified shippers are a solution to the project
5	Team meeting to confirm design draft (return to "drawing board" if team not satisfied)
6	If using a vendor pre-qualified solution go to step 8, if not continue to step 7
7	Perform design verification as per company policy
8	Perform operational qualification per company policy
9	Perform performance qualification per company policy (if required)
10	Document all steps and provide report signed to Quality for approval
11	Implement packaging shipper solution

Since sustainability is something the company is interested in, during step 4 of the process, engineers will consider eco-friendly solutions and reusable containers as opposed to one time use containers; engineers will also receive feedback from patients that will enable better future designs.

Taking into account all the results discussed, the team focused around one metric to ensure the new process was improving from current process. The metric, titled Rework Metric, is measured by the amount of iterations performed in step 8. The thought process is that if all the right information was communicated prior to step 8, then only one iteration of step 8 would be needed for the project. The target for the Rework metric is that the number of times step 8 is executed is only one time. There isn't a formula for the metric, it's just as described, and captured in team meeting minutes.

Pilot Run

During the pilot run of a cold chain project for the purpose of this project, the team found the process to work very well and the definition of roles and responsibilities helped ensure each team member knew what their expected contributions were. There were 2 iterations of step 5 which increased value as all information brought forward was value adding and furthermore helped identify a missing requirement from the process that has now been incorporated which was "amount of product desired per container" as this was the missing link which triggered the second iteration of step 5. The team moved forward and executed steps 7 through 9 per company policy and only one iteration of step 8 was performed. The team is currently in step 10; documenting in our internal policy documents the design specifications.

Future of Cold Chain

As a result of this research, the cold chain engineer will focus on how future shipping containers can be more sustainable eco-friendly solutions which involve reusable containers/shippers. As more and more drugs come out that require cold chain, vendors are coming out with prequalified solutions which make the cold chain process a lot quicker for each product if it can indeed use a prequalified option; a conscious effort will be made to find pre-qualified solutions which help keep costs down also. As cold chain evolves into temperature control management, the engineer

will be sent to several training seminars to understand the complexities around regulations and room temperature control requisites. Moving forward the team knows that in a short time, it will no longer just be about products that need to be kept cold, but also looking into room temperature control and frozen shipments. Lastly, the cold chain engineer will also seek new technologies which can help create more robust cold chain/temperature control solutions. The advent of phase changing materials (PCMs) and all the new capabilities they bring to cold chain packaging will be considered while also requesting more inputs from the end users to align with their expectations and improve customer satisfaction.

CONCLUSION

In conclusion, this project has been successful in completing its objective of reducing rework caused by missing requirements. In the past, several iterations would have been performed in order to arrive at the desired design for the shipper and in the pilot ran for the project only one iteration was needed for step 5 and the team is currently in step 8. The team successfully defined the roles and responsibilities, established the requirements of information needed for each project, produced standardized process steps that can be replicated and used in each cold chain project moving forward and created a metric to measure rework. As the team sets it sights in the future of cold chain in the company, it knows it will have to work in incorporating sustainability and increasing its team scope to add controlled room temperature and frozen temperatures to the cold chain program which might produce a change to the program name.

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