Packaging Coordinators Inc.

Overcoming research challenges with Adaptive Trials

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Summary

There has been cause for concern within the pharmaceutical industry over the last five years, regarding increasing research and development costs, combined with a fall in the number of new drugs brought to market. In an attempt to overcome this issue there has been a significant rise in the use of adaptive clinical trial designs, whilst saving time and money as well as facilitating more effective decision making,. One of the biggest challenges that pharmaceutical companies have experienced has been delivering compliant clinical trials supplies across diverse patient populations in the relatively short timeframes that adaptive trial designs require, remaining focused on ensuring that patient compliance and product quality is in now way compromised. This demand has led to the launch of fast response services that support Research and Development in responding to changing dosing regimens mid-trial.

Existing Challenges

In adaptive trials, sponsors continually re-evaluate their methodology using interim data analysis. This regularly results in significant changes being made to the study as it progresses, changes often include making alterations to the dosage level of a particular drug. Analyses occur under very tight timelines and as a consequence, only last minute decisions can be made on dosage levels throughout each phase. It is imperative that pharmaceutical companies are able to fulfill demand for new dosing combinations fast, accurately and in accordance with comprehensive regulations. New formulations can also take a significant amount of time and retesting, meaning that study directors need innovative ways of defining a dose without re-formulating each time.

An additional significant challenge in adaptive trials is ensuring efficient distribution of materials. Ensuring compliant shipments of investigational products to numerous different study sites of course poses a significant challenge. There is a requirement to ensure that Good Clinical Practices (GCP) and Current Good Manufacturing Practices (cGMP) are adhered to, as well as the revised Good Distribution Practice (GDP) guidelines published by the European Commission on the distribution of medicinal products in the EU.

Another essential part of this process is to ensure that tracking of the drug, throughout the clinical trial life cycle, takes place. In addition to this there is a requirement to ensure that there is a reliable and efficient accountability process, so that unused product may be reconciled, returned and destroyed.

Regulatory Outlook

In 2004 the United States' Food and Drug Administration (FDA) launched its Strategic Path Initiative to change the way drugs are formed and brought to market[1]. This particular initiative is aimed to counter the dangerously high levels of attrition in the clinical stage of development; it will also allow the investigator the flexibility to identify the optimal clinical benefit of the medicine under trial, whilst

[1] Parke, Tom. (2008). *Making adaptive clinical trials mainstream.* Available: http://www.clinicaldiscovery.com/readArticle.aspx?articleId=97. Last accessed 20th March 2012.

not endangering the validity of the study[2]. A scheme that falls within this initiative is the adoption of adaptive design clinical trials.

Case Study

An adaptive clinical trial is where the data collected during the study is monitored and analyzed whilst the trial is in progress. This provides the study directors and investigators with the option to adapt or re-design a trial after reviewing data close to the point that it was captured. As the design allows the opportunity to review results on a real-time basis, modifications can be easily implemented in order to improve the probability of a positive result. It can also offer the opportunity to stop the study if it appears to be ineffective. If used accurately, the adaptive designs have the potential to save time and costs by preventing the number of study failures. They also reduce the number of subjects required. As clinical trials designed with adaptive features have great potential to result in more efficient decision-making within a drug development programme, as well as offering an increased chance of answering the clinical question of interest, they are becoming an increasingly prominent feature within the R&D field.

Drug Supply Challenges in Adaptive Trials

There are clear flexibility and efficiency benefits of using adaptive study designs, however pharmaceutical companies are still facing many operational and logistical challenges if they are to be implemented effectively and with successful outcomes. Processes such as trial design, randomisation, data capture, trial supply and trial monitoring can all contribute major concerns and obstacles to investigators. Many of these issues exist within conventional formats, the problems become more explicit when placed within an adaptive setting where limited timeframes and changing parameters are common place, resulting in the requirement for highly-efficient processes to be implemented to manage demands.

A significant challenge for the industry is the clinical trials packaging and drug supply. Materials supply in adaptive trials can be affected by many different modifications including dropping or adding treatment arms, change in allocation to treatment arms, changes in planned sample size or dose groups and changes in primary endpoint.

To allow efficient management it is essential to ensure that sufficient supplies are available and packaged to meet the needs of the study. Precise planning and coordination of the activities of many different players is needed. In classic trial designs, the amount of material required is fixed and can be easily planned before the trial starts. A standard formula can be used to calculate how much of the drug and placebo/comparator have to be made available to accommodate all patients for the length of the study at the outset.

The Need for High Quality Services

It is currently quite common for the end-to-end clinical trials packaging process to touch many skilled individuals over multiple organisations and departments. This can lead to patient response driven, adaptive designs taking a lot longer than is necessary, thus causing avoidable hurdles and time-burdens. In order to address the newly emerging challenges, organisations specialising in packaging outsourcing, storage and distribution are offering an extensive line-up of services to pharmaceutical companies to support adaptive clinical trials globally. This is helping them streamline processes when reacting to changing needs mid-trial or adapting to country specific protocols.

Rapid response services have been introduced by innovative providers, to deliver compliant clinical trial supplies in the shortest time possible without compromising quality. In many cases this can be as little as just a few days. This enables pharmaceutical companies to outsource and give greater

[2] Gupta, K and Mahajan, R. (2010). Food and drug administration's critical path initiative and innovations in drug development paradigm: Challenges, progress, and controversies. *Journal of Pharmacy and Bioallied Sciences*. Oct-Dec (2-4), pp307–313

flexibility in managing the end to end process and the confidence of a provider who can react quickly to ever changing requirements by using rapid response teams of highly trained personnel with vast knowledge in all areas of supply who can conduct multiple tasks in a matter of hours. The systems and operating processes have workflows that provide a streamlined process whilst ensuring quality, thus enabling an immediate turnaround of defined doses when sponsors require them.

The industry is also seeing a growth in 'just-in-time' labeling, whereby unlabeled study materials have a study/geography specific label applied to them at the latest possible opportunity. Once a request has been received, a specific number of packs can be labeled at point of dispatch. Working with a specialist partner on this kind of project can be particularly effective as they have the capacity to handle bespoke batches at short notice and can activate fast and effective quality control processes to enable trial materials to be released and dispatched quickly.

Working with an experienced provider means that pharmaceutical companies can draw on experience across projects, making them well positioned to assist other clients in adaptive trials best practice. A number of providers offer state-of-the-art storage facilities dedicated to investigational medicines, offering extensive environmental controls and monitoring, and meeting full requirements for GCP, cGMP and GDP practices. In addition providers will often oversee returns management, storage and destruction of clinical trials material once the project is closed down.

Clinical trials supplies providers can greatly improve the efficiency of ingrained habits and processes by offering a fast pathway to radical improvements in productivity, cost and speed in clinical trials. By having the processes in place this allows sponsors to implement new and better methods, they can also benefit from partner's investment in people and infrastructure rather than investing the capital themselves. With continually increasing globalisation of clinical trials, it is essential that providers can demonstrate a broad geographic reach. A supplier that has a global presence and the facilities to store and ship goods throughout the world and under a variety of conditions, can enable companies to develop a detailed global supply chain strategy to keep sites supplied with materials.

The Future Landscape

Adaptive clinical trials leading to improved product development processes is attractive and many pharmaceutical companies have already put the strategy in place. These designs allow for increased patient safety, whilst also conferring benefits of reduced development costs and product time to market. Despite their wide-ranging advantages, there are potential pitfalls for every clinical trial, potential risks need to be taken into consideration when deciding what approach to use. It is likely that many companies will turn to all encompassing packages from third parties in order to avoid these issues.

Working with an expert packaging provider can support the management of a companies needs throughout the duration of an adaptive trial, this can be done regardless of its location and complexity. The services provided allow suppliers to be turned around immediately in response to clinical demand, reducing delays without compromising quality or knowledge. Working with expert partners will enable organisations to reap the benefits of adaptive trials with confidence that the potential pitfalls will be avoided.