

# Emphasis on Protocol Design Helps Alexion with Timeline Adherence

## Alexion Applies CTTI's Quality by Design Recommendations

### SUMMARY

Alexion applied Quality by Design (QbD) principles in the protocol development process for a phase 3 trial to register and file its second product. They met the tight timeline by uniting cross-functional stakeholders early in the process to build a streamlined, simple protocol. This resulted in a successfully launched trial that cleared regulatory approval and brought the product to market.

### GOAL(S)

Alexion was set to launch a phase 3 trial to register and file its second product. It was a pivotal make-or-break moment for the company, so getting the process right was absolutely critical.

### CHALLENGES

Alexion was a burgeoning company, systems and processes were still limited, and experience with phase 3 trials among the team was minimal. In addition, the trial's timeline was very short. And, as with many sponsors at the time, discussions around "quality" tended to be from an audit perspective rather than a proactive focus on risks.

### SOLUTION(S)

A new member of Alexion's leadership team had experience applying QbD, so she was selected to partner with the organization's vice president of Medical Development to pilot a QbD process for the pivotal phase 3 trial.

### TAKING ACTION

In alignment with CTTI's recommendations, Alexion established a steering committee to hold the team accountable for keeping quality at the forefront of discussions during study planning and ensuring team alignment. The team's development of a QbD steering committee not only served to guide the product's QbD journey, but also helped the team apply the QbD processes to a parallel indication for a compound that later emerged. The study team collaborated with operational colleagues, medical team members, investigators, and its CRO to understand potential difficulties in executing the study protocol. As a result, the Alexion team established four critical-to-quality (CTQ) factors for the study:

1. Ensuring enrolled patients have the opportunity to meet the primary endpoint before starting study drug
2. Ensuring compliance with drug therapies
3. Correctly stratifying patients within six stratification buckets based on two different factors that would affect their response to therapy
4. Prevention of patient drop-out

This multi-stakeholder collaboration was key to Alexion's success. For instance, one primary endpoint around transfusion avoidance had very specific transfusion criteria to which investigators had to adhere. Medical team members gave valuable feedback in their perception that this criteria would be complex and difficult for an investigator to comply with properly. That input drove a decision to check patients' hemoglobin levels prior to randomization, and avoided a situation where study participants could fail the primary endpoint before starting the study drug.

The multi-stakeholder team had a meeting every month during which they put together slides with CTQ factors, and then diligently tracked them.

- For these meetings, clinical trial leads assembled the data, and worked closely with the Quality function. The study team kept track of associated metrics, and whenever they saw a potentially challenging event, they collaborated on how to prevent further events from occurring.
- Because of the trial's pivotal nature and strict thresholds for missed doses, the team monitored the study aggressively, including having medical monitors visit multiple sites, and many visits to high-enrolling sites.

### IMPACT

The trial met its timeline, and when the U.S. Food and Drug Administration approved the investigational product, the news was met with celebration across the organization. In an all-hands meeting with the Alexion's CEO, every single product team member mentioned quality as a critical driver to the trial's success. An organization that once saw quality as a tick box to be checked was transforming into one with a holistic quality perspective and individual ownership across the enterprise. This change, Alexion's leaders say, is the true value of implementing QbD. The study had zero protocol amendments related to CTQ factors, and the intense focus on these factors meant that none of them ever reached the thresholds the team deemed problematic.

### ADVICE


From this team's perspective, there is nothing about QbD that needs to slow down the timelines. It is not a rate-limiting step. For example, if a team does not identify CTQ factors at the protocol concept sheet stage as CTTI recommends, it is not too late. The team can still identify them, and associated strategies for addressing important risks, with as much rigor and thought as possible, even if it is later than ideal. QbD is meant to help teams, not hinder them. Alexion has since evolved its QbD processes to better serve its needs. For example, product-specific QbD steering committees were disbanded in favor of portfolio-wide risk-based quality management steering committees that ensure the quality approach is calibrated across all products. These teams include development heads for therapeutic areas, as well as leaders from regulatory, clinical operations, quality, and data management. Each drug program in the company also has a quality steering committee, which includes the product team lead, quality operations leads, and more. In a recent Good Clinical Practice inspection, the organization's approach to quality was commended as one of the most mature and thoughtful the

inspector had seen.

## **ORGANIZATION**

Alexion Pharmaceuticals

## **CONTACT**

Prajna Kumar 

## **ORGANIZATION TYPE**

Industry

## **IMPLEMENTATION DATE**

2016

## **TOPIC**

Quality

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