

Clinical Endpoint ANDA Program Optimization

White Paper Series Introduction



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Foreword

This introduction marks the launch of a series of White Papers dealing with the optimization of Clinical Endpoint ANDA Programs for the generics and specialty pharmaceutical industry. We will be publishing these reports addressing and analyzing different aspects of optimization several times a year and making them available on our website, at marketing and technical conferences and through other established electronic publishing services.

A majority of ANDA clinical studies involve evaluating systemic drugs that are delivered into the blood stream and then distributed to specific sites of the body. Bioequivalency for systemic drugs is normally determined through conducting pharmacokinetic (PK) studies. However, there are some drugs that are not intended to be absorbed into the bloodstream (locally acting drugs). They often require Clinical Endpoint (CE) studies in order to prove their bioequivalence. These locally acting drugs typically are delivered directly to the sites of action in the skin, mouth, eyes, ears, nose, vagina, urinary tract or gastrointestinal tract.¹

biorASI has been focused on CE ANDA programs for a number of years. Every CE ANDA program we undertake provides us with new insights into varying aspects of these complex clinical trials. As we analyze the specific issues and questions raised by these studies, we continuously improve our overall ability not only to optimally resolve a single issue, but also to optimize the overall process and the entire program itself.

We owe our knowledge and ability to optimize CE ANDA programs to our sponsors and to the generics drug industry as a whole. It is only natural to share some of the knowledge we have gained as well as the approaches we have developed with the industry. To that end, we have written these White Papers. We trust you will find them not only interesting reading, but also a source of new ideas and approaches to vexing problems. We invite your comments, critiques, suggestions and overall participation. It is our sincere hope that these papers will grow into an open forum to explore and spur exciting future developments in our industry.

Boris, Grigor, Chuck and Lindsey

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Introduction to Program Optimization

Clinical Endpoint ANDA trials represent a very significant expense for sponsors in both time and money. The entire process is a series of choices, decisions and tradeoffs that begins with deciding which drugs to develop and continues throughout the clinical development process. Generic companies that are accustomed to the shorter and less expensive PK bioequivalence trials may encounter an entirely different spectrum of issues in CE programs and may well experience difficulties in analyzing and making the new kinds of decisions required by CE studies. These trials often require many hundreds, and frequently thousands of patients. They can easily last over a year, cover many clinical sites and often span a number of countries and regulatory jurisdictions. It is easy to see how and why the ramifications of such decisions are very significant.

The issues and compromises start right at the beginning of the initial evaluation process of potential ANDA programs that require CE clinical studies. As sponsor companies' executive committees sit down to discuss potential programs, it is the costs and time of the overall program, not the ability of the formulators to produce appropriate results that frequently takes center stage. After all, that is where initial estimates could vary not by just hundreds of thousands of dollars, but sometimes by millions.

In this White Paper Series, we will be examining the types of decisions that generic and specialty drug companies face every day. While we will be dealing primarily with the clinical development areas of a sponsor's CE programs, we also may explore other areas ranging from initial program planning all the way through marketing and distribution. We might also touch upon the optimization of CE 505(b)(2) NDA Programs that are commonly closely related to ANDA.

Using a top down approach, we will investigate the various questions, issues and possibilities that can arise while planning and executing a CE program and then explore the answers, criteria, methodologies, processes and solutions required to ensure:

Following this introduction, the next two papers will take an in depth look at:

- How to select the optimal number of patients for CE ANDA clinical studies, and
- How to select the optimal amount of a Reference Listed Drug (RLD) to be purchased for a CE ANDA clinical study.

Additional papers dealing with optimizing other aspects of CE ANDA programs will follow at regular intervals and will be available through our website and at industry technical and marketing conferences. Titles currently under consideration include:

- Reducing Trial Induced Variability To Increase Probability Of CE ANDA Trial Success,
- How To Optimize Selection Of The Patient Population For CE ANDA Clinical Trials,
- Optimization Of Clinical Trial Logistics In Multi-Country CE ANDA Studies,
- How To Optimize CE ANDA Study Regulatory Approvals In Multi-Country Environments,
- Optimizing Study Randomization Schedules To Achieve Required Superiority And Bioequivalency With A Minimal Number Of Subjects,
- Correlation Of Pharmacokinetic BE Data And Clinical Equivalence Conclusions,
- Designing Studies Aimed At Demonstrating Equivalence To Two Reference Formulations (For Example, In Different Countries),
- ANDA Suitability Petitions Vs. 505(b)(2), and
- Regulatory And Ethical Aspects Of Placebo Use.

We certainly welcome your contributions to the process and invite not only your suggestions for topics, but also your specific comments and general feedback. To participate, please email us at whitepaper@biorasi.com.

*The highest probability of trial success
at the lowest cost in the shortest time.*

Examples of CE Program Areas and Issues for Optimization

Once a target drug product has been identified, the development of a protocol synopsis is perhaps the most significant way to begin exploring clinical development optimization. This important document address the initial set of questions that usually arise when considering or planning a CE ANDA clinical trial, and may include:

- Expected number of subjects to enroll, Intent To Treat and Per Protocol,
- Key Inclusion and Exclusion Criteria,
- Study Objectives and Clinical Endpoints,
- Number of sites and expected locations,
- Study drug dose and method of administration,
- Study visits and duration.

Aided by the synopsis, the sponsor can then begin to make and implement the hundreds of decisions related to planning and running a clinical trial in a more informed and optimized manner. Such an approach can go a long way toward ensuring overall program success.

Optimization Criteria

Our approach in these White Papers is to first break down the questions or issues related to CE ANDA studies into their component factors, then examine how they are derived. Next we explore the consequences of manipulating them and determine what effect that will have on the outcome. Depending on the evaluation and optimization techniques we choose, we then select specific criteria to help us to determine how well we are doing in meeting our optimization objectives. Typical criteria might include:

- Quality
- Time
- Acceptance
- Cost
- Service Level

In and of itself, each of these criteria is a very important measure of how well we are optimizing certain elements of the clinical program, but when taken and measured together, they represent real optimization.

The Optimization Process

We've used the term optimization on several occasions. Let's take a closer look at what we mean by it. Optimization is the process of modifying a system or processes within that system to make some aspect of it work more efficiently or use fewer resources.

Optimization consists of choosing the best from a set of available alternatives, with a goal of making the system as efficient as possible in some defined sense. In the specific case of CE ANDA programs, the primary objectives are to make the process as resource-efficient and cost-effective as possible, while increasing the likelihood of a successful outcome.

That process consists of finding the best solutions to the issues under consideration, separately and in combination, determining their influence (either positive or negative) and then calculating the optimum value of those variables to build into the protocol, procedures, logistics, approaches and other elements of the trial.

We often begin the process intuitively by reasoning how this or that variable or potential element of the solution influences the criteria. But at the end of the day, you need measurements. It is our intention to examine the details of this process in each of the White Papers in the series as they relate to the specific problems being solved.

*"If you can't measure it,
you can't improve it."*

- Lord Kelvin

Multidimensional Optimization

Looking at each criteria and determining which variables may affect it is really just the beginning of the optimization process. The key to more complete optimization comes from examining each variable to determine how it affects all criteria concomitantly, and then to establish the optimum value of that variable for the trial as a whole. For example, as we vary the number of patients in the trial in order to achieve optimized levels of criteria such as time, cost and the probability of success, we also influence the number and location of sites. This, in turn, can affect the service level and the trial result acceptance. And that's just looking at a single variable. Clinical program optimization involves numerous decisions relating to numerous variables as well as evaluations against numerous criteria.

The White Papers in this series will be examining both single-issue optimization as well multi-issue and multi-criteria views. We will also endeavor to make all of the optimization exercises (many of which have come from actual real life situations) as simple and as practical as possible.

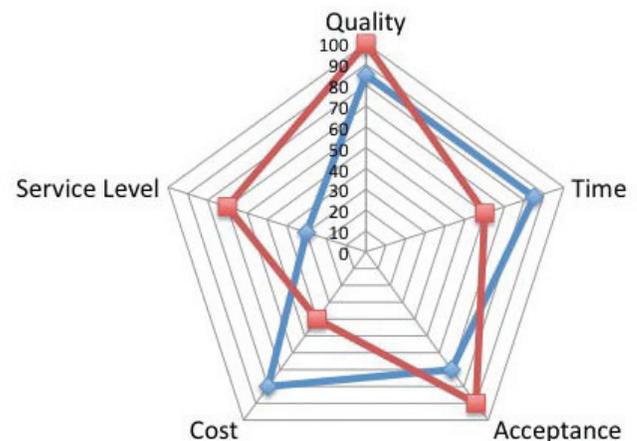
The Series will also share our experiences as well as the techniques we have developed relating to solutions that provide the lowest cost, highest quality and most efficient use of resources, all while optimizing trial success probabilities and outcomes.

Visualizing Optimization

To better illustrate and envision the results of our decisions, we use a tool called a Radar Chart that combines several different criteria all used for measuring the outcome of a decision. Radar Charts have multiple axes along which the relative values of each of the five criteria used in a given optimization process can be plotted. A point close to the center on any axis indicates a low value. A point near the edge is a high value. Sometimes the lower value is preferable (such as cost or time) and sometimes it is the other way around as we try to maximize the value (such as quality or acceptance).

The Radar Chart below shows our five chosen criteria as they relate to a typical solution of some specific issue in the trial to be optimized. The blue plot shows the key criteria under one solution; the red plot, another. Needless to say, you would choose the red solution as the preferred one.

In real life decision making, the answers might not be as clear cut as in this example, as time or costs might be better in one decision while the probability of trial success (quality) may be better in another. Selecting the best or most correct solution under those circumstances is the objective of the optimization processes and how that is done is what this White Paper Series is all about.



“Quality is never an accident; it is always the result of high intention, sincere effort, intelligent direction and skillful execution; it represents the wise choice of many alternatives.”

- William A. Foster

Optimizing CE ANDA Programs

We have purposely defined each of the criteria we may use with a broad brush; having discovered that such an approach opens many more possibilities for optimization than a narrow view. And, of course, in addition to examining these optimization criteria separately, we will be exploring them in combination.

Quality

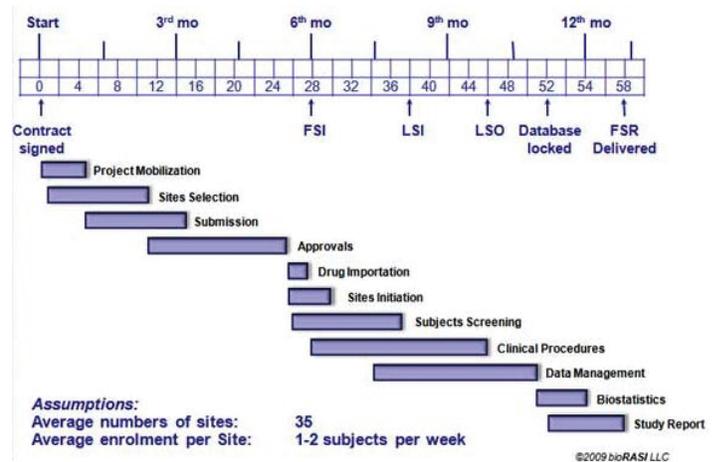
It is easy to think of quality just in terms of adherence to Good Clinical Practices (GCP), the protocol or regulatory compliance. But to do so would be to significantly limit the opportunities for process improvement and thus, program optimization. When it comes to defining increased quality in clinical development, it is imperative to consider increasing the probability of trial success.

In our planned White Papers, we will be addressing many avenues for improving the probability of trial success, including some that do not increase either cost or time, such as reducing trial induced variability.

Time

There are few areas where the axiom, “Time is Money” is more true than in clinical trials. And while the protocol plays an important role in determining the length of certain trial procedures, such as the time from First Subject In (FSI) to First Subject Out (FSO), there is still a great deal of room to optimize the timeline. This becomes especially relevant if you consider the time prior to recruitment, the time recruiting takes and the time after the clinical procedures are completed as significant parts of the overall time component.

Our White Papers will examine project planning and project management tools and techniques that can cut overall time requirements by minimizing the time of certain specific tasks, such as regulatory approvals or recruitment. We will also share some experiences we have had in running tasks in parallel or ahead of sequence (as shown below).



Acceptance

Although the issue of acceptance is usually thought of as relating only to the development of novel drugs, in many ways, it is just as important for generics. Acceptance by the regulatory agencies, the industry as a whole through opinion leaders and by patients can not be ignored as areas for optimizing CE ANDA programs.

An example from the 2009 GPhA technical meeting makes this point well. At the conference, representatives of the FDA’s Office of Generic Drugs (OGD) clearly conveyed what amounted to their preference of not seeing 100% of future dermal CE ANDA trial sites located in India. That preference has led to industry discussions that may spread beyond just dermal trials. OGD preferences should be taken to heart in any program’s optimization efforts.

Future White Papers will address these issues and provide techniques for increasing the level of acceptance of trial solutions without necessarily increasing overall expenses related to time and cost.

“There is nothing so useless as doing efficiently that which should not be done at all.”

- Peter Drucker

Cost

Of course, the ability to minimize costs in a clinical trial is a given. But how can that be accomplished without putting some other criteria in jeopardy? Taking shortcuts or cutting corners can endanger a trial or significantly lower the chances for timely approval. Even worse, it can decrease the probability of trial success and put the entire program investment in peril.

Future White Papers in the series will address these very significant issues by offering approaches and methods that can reduce overall cost while increasing service levels, quality, acceptance and reducing time. One such method involves optimizing major cost variables such as amount of RDL needed for a trial, which can serve to lower costs without affecting service delivery. We will be publishing a White Paper on this specific issue.

Another method we will explore in future White Papers will deal with reducing trial induced variability in order to increase the probability of trial success, reduce overall trial cost or both.

Service Level

Sponsor / CRO / clinical site / PI / patient relationships can take many forms. Managing those relationships in such a way that a sponsor is ensured of having real time, hand on the pulse visibility, without being overburdened, is the ultimate objective of having optimal service levels.

Success in achieving that goal depends on the experience and expertise of each party, specific program requirements and the approaches and techniques used. This is where the CRO role goes far beyond merely fulfilling the sponsor's protocol and monitoring the trials. Depending upon the level of the sponsor's in-house resources and preferred operating procedures, the CRO can play a pivotal role in creating an optimized program, beginning with a Protocol Synopsis and continuing all the way through biostatistics and report writing. And, of course, all while maintaining the aforementioned optimal service level.

Since the sponsor makes or approves all major decisions in every trial, but the CRO implements them, the importance of optimal communication between those parties cannot be overstated. Add to that the multinational, multilingual aspect of most trials, and the need for high quality communication and optimal service levels becomes even more important.

Many of our Papers will be exploring how to optimize the trial participants relationship through effective communication techniques and teamwork. Other Papers will address additional important aspects of Service Level relating to real time visibility and communication.

Looking Forward

In this Introduction, we have only skimmed the surface as to what program optimization is and how it works. In future Papers we will delve deeply into how the optimization process works in specific areas of CE clinical trials, with an emphasis on the practical aspects of answering the most important question: *"How can I ensure the highest probability of success of my CE program at the lowest cost and in the shortest time?"* We look forward to making the journey together.

"The single biggest problem in communication is the illusion that it has taken place."
- George Bernard Shaw



CLINICAL RESEARCH OPTIMIZED™

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Biorasi is a contract research organization (CRO) widely recognized for delivering success in complex clinical trials. This is possible through TALOS™, an innovative operating model that unifies systems and teams with a powerful project management methodology to ensure high quality delivery. Overall, Biorasi balances power, time, acceptance, cost and service level to optimize the delivery of clinical studies.

Global biopharmaceutical companies have come to depend on Biorasi to deliver their most complex studies. The company's expertise includes a range of molecule types, development phases, therapeutic areas, geographies, and development programs. Biorasi has collaborated with sponsors to enable FDA, EMA, and multi-venue approvals for numerous small molecules and biologics. Biorasi, headquartered in Miami, Florida, maintains office-based teams around the globe. The company has received the coveted CRO Leadership Award from Life Science Leader magazine and has placed on the Inc. 500 list of America's fastest growing companies.

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