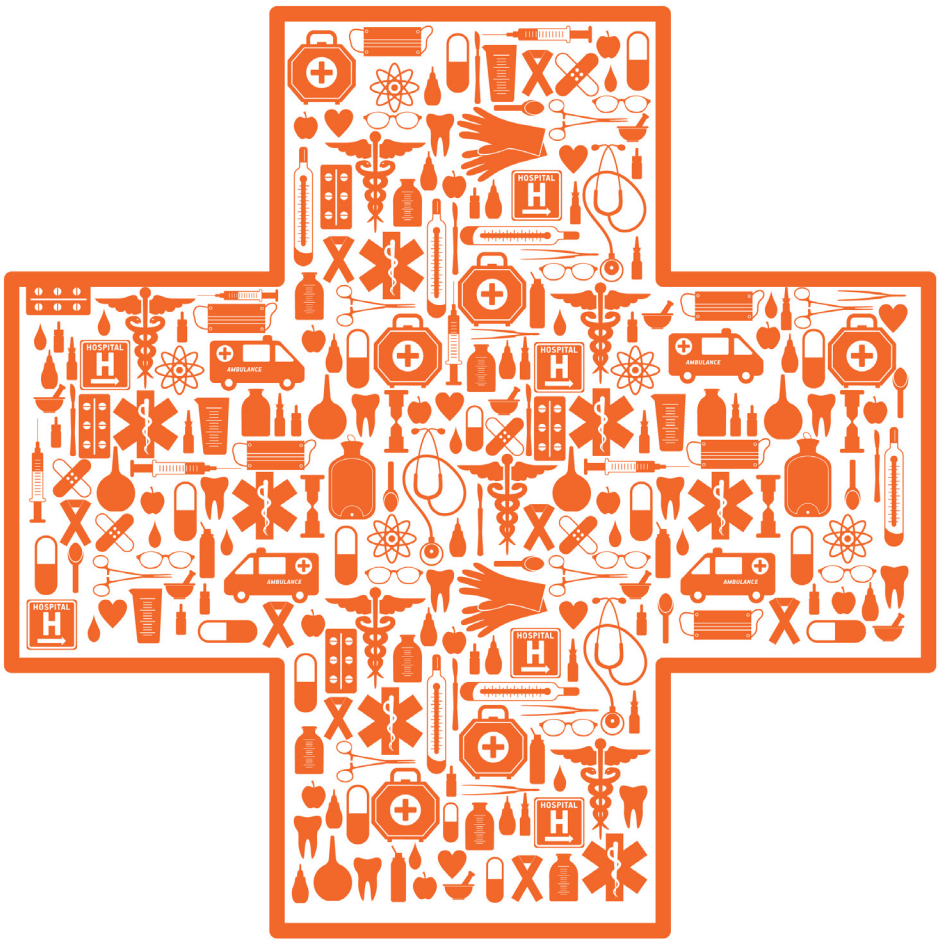
Optimizing the Amount of Investigational Materials in ANDA Studies - Part Two

For Dermal Semisolid Clinical Studies
White Paper Series



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Introduction

Optimizing Clinical Endpoint (CE) ANDA studies demands intense discipline and planning, addressing every potential variable involved from study design all the way to FDA submission for approval. Minimizing costs while ensuring the highest probability of trial success is of paramount interest to specialty pharmaceutical companies. Following the investigator site costs, the next greatest expense is that of the Reference Listed Drugs (RLD), which can account for up to a third or more of the overall budget, thus imposing significant economic impact when conducting Phase III clinical trials.

In our previous white paper titled, “Optimizing the Amount of Investigational Materials in ANDA Studies – Part I,” we brought this issue to light and offered a roadmap for calculating the amount of investigational material and RLD required for various ANDA programs. This white paper presents Part II, a plan which highlights the magnitude of impact that effective RLD supply management plays in optimizing CE dermal semisolid studies, perhaps the most complex and costly types of ANDA trials. The scope of this white paper covers many issues woven into the optimization process, but not all of them can be delved into with extensive detail. Numerous aspects of trial optimization will be identified here and addressed in future white papers.

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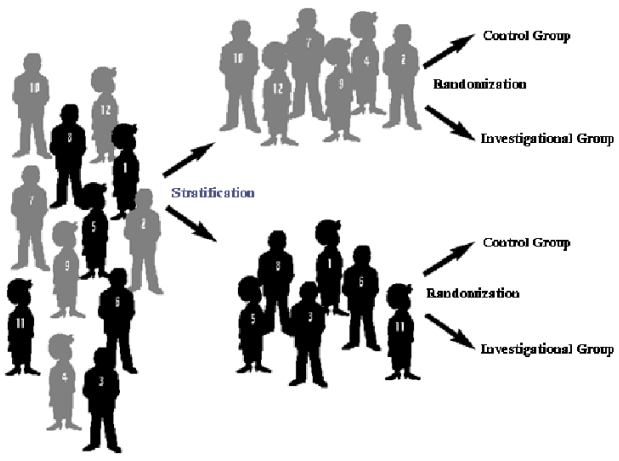
Financial Impact

The cost of the RLD in a clinical trial is often overlooked or seriously underestimated. Semisolid formulations for CE dermatological studies for example could run from a few hundred dollars to one-thousand dollars per tube. Bearing in mind that a reference treatment group typically makes up between 25% to 50% of the total study population, often exceeding 1,000 patients in CE ANDA trials, Sponsors will likely spend from several hundred thousand dollars to well over one-million dollars on the purchase of RLD product alone. Thus, a miscalculation of just 10% of the amount of RLD required can result in either excessive waste of precious dollars or worse, costly delays and potentially subjecting the entire trial to fail. Erring on either side could be disastrous.

If failing to accurately determine the correct amount of RLD required for the study can mean the difference between a successful trial and total collapse (or at the very least a $250,000 mistake), Sponsors have no choice but to rigorously scrutinize a broad array of variables during the study planning process.

To an experienced CRO it makes obvious sense to optimize the process of calculating and planning RLD supply management, ensuring sufficient quantities to carry out the entire trial without delay, certifying accurate retention of samples for the FDA per regulatory requirements, and accounting for the myriad of variables that play a part in challenging the success of a clinical trial, all while minimizing the potential for wasted resources.



The Starting Point

We have previously addressed in detail the importance of subject number calculation in our white paper, “Patient Numbers Required in Clinical Endpoint ANDA Trials.” While the number of study subjects is one of the key factors in determining the optimal amount of RLD for CE topical studies, it is merely the first and simplest step in a series of factors to consider.

Progressing from a starting point of the per protocol subject number and continuing through the clinical design path to the goal of determining the ultimate number of RLD units to purchase is not as straightforward a process as one would initially believe. To help illustrate a comprehensive planning process, Figure 1 presents a simplified schematic accounting for many of the variables to be contemplated and quantified.

It is understood that the per protocol (PP) number includes only those subjects who are expected to complete the entire treatment program and is the primary factor in determining the optimal amount of reference listed drug for CE topical studies; yet there is a series of coinciding dynamics affecting drug supplies that, if disregarded, can derail the entire study.

Clinical protocols usually provide the number of subjects for PP, Intent to Treat (ITT – all subjects who start receiving medication and have been evaluated at least once, but do not necessarily complete the trial), and Enrolled Subjects (ES – the number of enrolled or randomized subjects selected at the beginning of the trial). Enrolled subjects represent the gross number of subjects prior to dropout rates. A superior CRO, biostatistician, Principal Investigators (PIs) and opinion leaders experienced in topical indications are qualified to determine optimal subject population estimates and dropout rate assumptions. Due to the complex nature of ANDA trials, CE topical studies such as dermatology trials commonly call for between 400 and 1,500 enrolled subjects.

The total RLD to be purchased must be sufficient to treat the reference treatment group of the PP subjects; however, because there is a typical 5-25% dropout rate from the ITT subjects, the RLD purchase must still accurately account for this group.

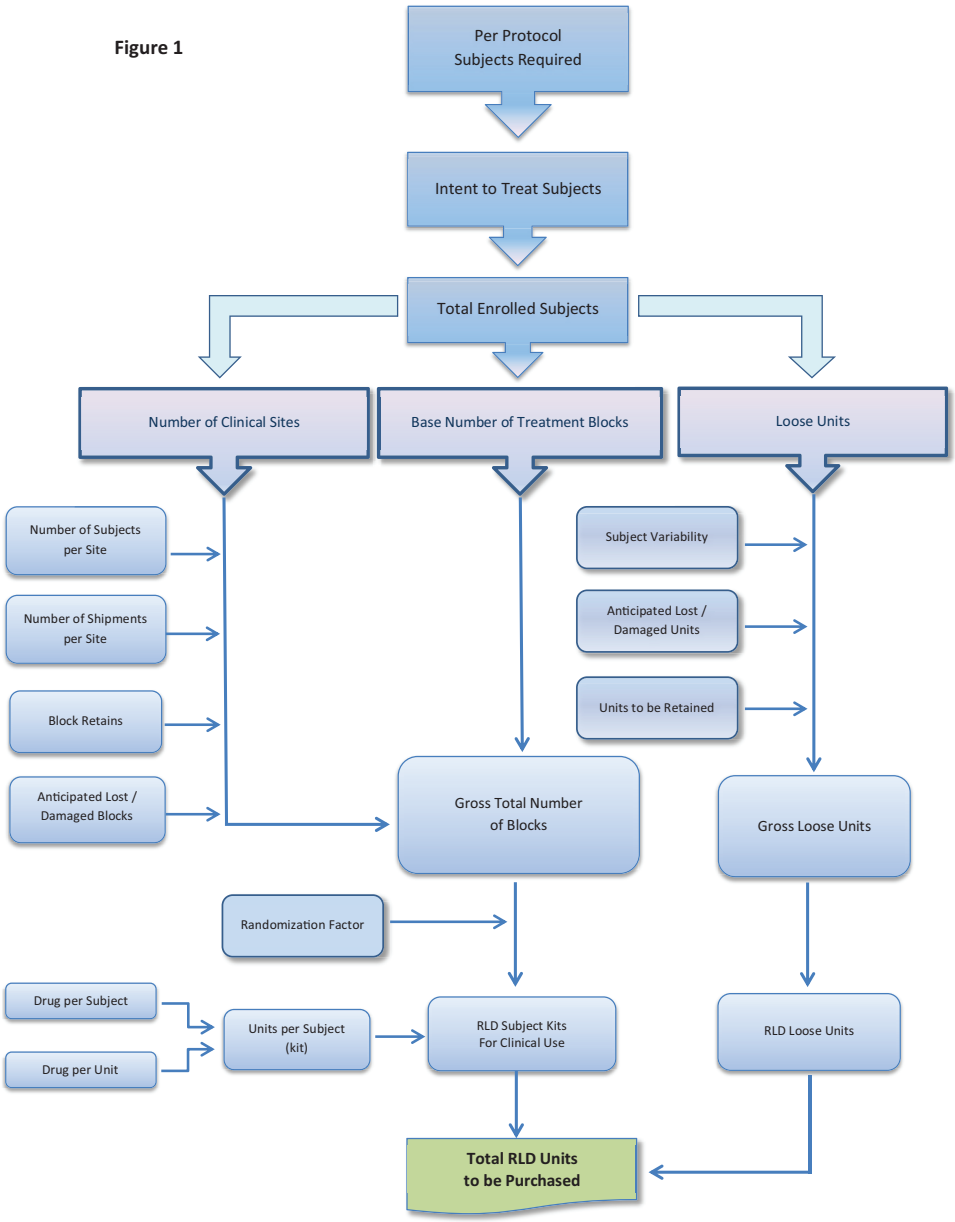
ITT subject numbers are best estimated by a CRO with extensive experience with a variety of dermatological indications. The ITT population is similarly derived assuming a 5-25% dropout rate from the number of enrolled subjects. Managing the dropout rates to minimal values plays a critical part in minimizing wasted supplies and drug costs.

To ensure proper calculation one must begin with the PP and work backwards to the estimated ES as follows:

PP / (ITT % retention rate) / (ES % retention rate) = ES
For example:
where PP = 900
ES = 900 / .85 / .80
ES ≈ 1,324

At this point of the decision tree there are numerous branches to be simultaneously evaluated. The schema in Figure 1 outlines a number of factors and considerations, each of which will be expanded upon.

Figure 1



Clinical Sites and Treatment Blocks

Enrollment projections are a function of the CRO's ability to determine the number, locations and quality of clinical sites to be selected for participation in the study. The number of study sites can be optimized by evaluating several variables including, among others, estimated enrollment rates per site, the duration of the desired enrollment period, the length of the study, and the probable recruitment factors.

The number of sites and their distribution across various countries directly influence the number of shipments needed and the RLD amount to be purchased. While accelerating patient recruitment is a prevailing objective in large studies, there is a delicate balance to this aspect of the study design. Inclusion of too many sites may increase the possibility of excess RLD at the conclusion of the trial resulting from projection errors being magnified. At the same time, having too few selected sites may put the trial at greater risk of falling short of enrollment requirements, failing to meet the protocol requirements, thus prolonging the study and driving up costs or possibly jeopardizing the trial success.

While dropout rates intensify potential cost over-runs, mismanaging the number of subjects per site will further compound the overage when the randomization factor is not precisely adhered to from site to site. One broken block (defined below) of investigational material across 30 clinical sites, for example, could exceed $100,000 in RLD alone. A resolution to this issue is to send more frequent shipments with less drug in each shipment. This can lead to a result of less waste of RLD, however more retains and higher total shipping costs.

Kits, Blocks and Loose Units

The coordination of services between the CRO and its contract pharmaceutical manufacturer handling the assembly, blinding, and distribution of the drugs will help to mitigate if not eliminate potential waste at the front-end of the drug supply chain. Employing technological expertise and precision, the RLD, test drug, and placebo are packaged into kits, blocks, and loose units to be delivered to the clinical sites around the globe in a streamlined process.

Kits

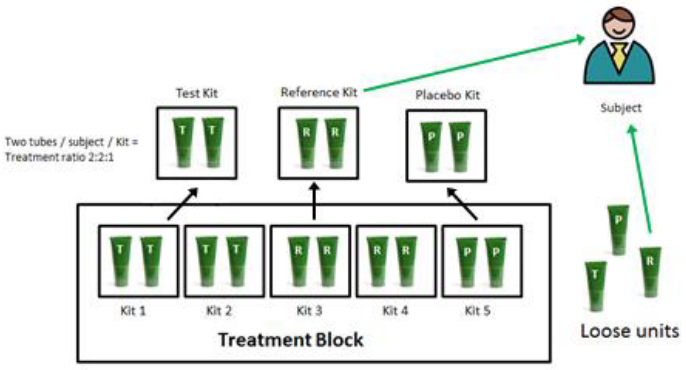
A kit includes the full amount of drug needed for one subject over the entire course of a clinical trial. In dermatological semisolid trials, kits are often comprised of tubes of ointment or cream and as such will have a certain amount of unrecoverable or inaccessible drug, which must be accounted for in calculating the number of units to include in each kit, whether it is the RLD, the test drug or placebo. The kits are arranged in blocks and are distributed to a group of subjects that meet similar inclusion and exclusion criteria such that pharmacokinetic and/or clinical evaluation comparisons can be made.

Blocks

A block consists of a set of kits for several subjects allocated according to the randomization schedule. Randomization is maintained by shipping the drugs in blocks of kits where the type of drug in each kit is anonymous. For example if the randomization is 2:2:1 each block contains two treatment kits for the two subjects in the test group, another two kits for the two subjects in the reference group, and finally one kit for the one subject in the placebo group. Now we begin to recognize increased potential for possible excess with insufficient attention to, and management of, subject numbers and dropout rates. The question then becomes, how many blocks to send in each shipment to the site. This number depends on a strategic decision from the Sponsor and CRO to reduce the amount of wastage and cost of RLD, along with shipping and handling expenses. . Since these factors differ from site to site, it will be necessary to make the determination on a site specific basis.

Loose Units

Loose units are extra individual units, tubes for example, required to be on-hand at each site in case extra units of the RLD, test drug, or placebo are needed. They are not part of a preassembled kit or block. Having loose units available eliminates the need to break down complete blocks and avoids delays associated with having additional units, kits, or blocks assembled and shipped from the pharmaceutical depot when a site might need just a few extra tubes of the RLD for example. Minimizing the number of required shipments plays a significant role in cost reductions as well. Ensuring optimal supply chain management between the depot and clinical sites is a science unto itself and may be presented in a future white paper delving into issues such as temperature-controlled storage, inventory management, kit assembly and distribution logistics.



Subject Variability

Loose unit demand is often the result of variables in human behavior, which can be mitigated by proper training at many levels including the PI, clinical coordinator, and the subjects themselves. In contrast to systemic drugs, topical drug delivery depends on the size of the subject, the size of the affected area, varying application methods used by individual subjects, and how much RLD drug is unused due to it being unrecoverable from the tube or packaging. These drugs are typically self-applied instead of being administered by trained staff and the specific protocol for things such as the number of applications per day and the coverage may not be followed consistently. Determining the amount of drug required per subject is a major variable in this equation. Yet, precisely calculating the amount of drug per subject (illustrated below) is only part of this issue.

The objective is to be able to optimize consistency and uniformity of topical application among 1,500 subjects in order to predict investigational material usage. Despite the best training, there are still circumstances that must be accounted for in estimating drug supply needs. Another example that needs to be factored into the equation is lost or damaged material in the subject's possession.

Planning to have enough of the investigational material in each kit to sufficiently accommodate every potential subject – regardless of body size and treatment area – goes beyond logic and is sure to result in significant unused surplus for a majority of subjects at the end of the trial. In a normal distribution of subjects, the Sponsor and CRO should aim to ensure each kit is sufficient to fully treat all subjects inside the bell curve at a specifically designated percentage. For example: if the kits are assembled with 6 tubes, which is sufficient to fully treat 85% of all subjects, the outliers beyond this point could be accommodated through dispensing loose tubes as needed without excessive waste across the entire study population.

Treatment-per-Subject Calculation

Presented here is an example for calculating the treatment per subject. The following assumptions are obtained from general subject information, the protocol, and the package insert for a Psoriasis medication:

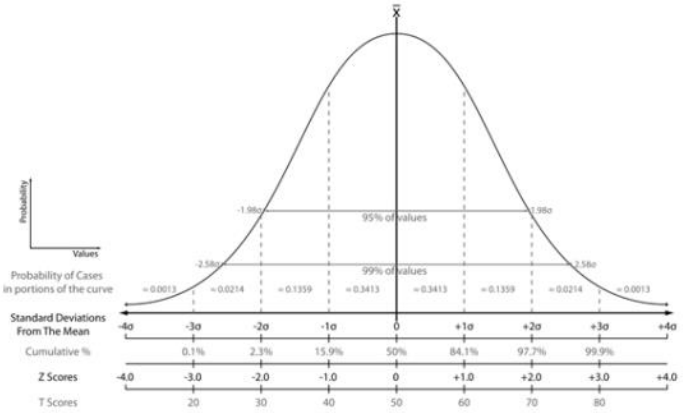
- Affected body surface (%) = 10 %
- Average body surface (sq m) = 1.8m2
- Average body surface (sq cm) = 18,000c m2
- Amount of drug per surface (mg per sq cm) = 2
- Applications per day = 2
- Number of treatment days = 56
- Amount of drug per tube = 100 g
- Unrecoverable amount of drug in a tube = 10 %

The first three items determine the affected body area, the second three determine the amount of drug per treatment per area, and the last two the usable drug in a delivery unit or tube.

The following formulas are used to derive the minimum amount of treatment needed for one subject throughout the study based upon the above assumptions:

Affected body surface (sq cm) = Average body surface (sq cm) * Affected body surface (%) = 18,000 * 10 % = 1,800
Amount of drug per application= Affected body surface (sq cm) * Amount of drug per surface (mg per sq cm) = 1,800 * 2 = 3,600 mg
Amount of drug per day= Amount of drug per application * Applications per day = 3,600 * 2 = 7,200 mg
Amount of drug for treatment per subject = Amount of drug per day * Number of treatment days = 7,200 * 56 = 403200 mg = 403.2 g
Usable amount of drug per tube = Amount of drug per tube * (100% - Unrecoverable amount of drug in a tube) = 100 g * (100% - 10 %) = 90 g
Number of tubes per subject = Amount of drug for treatment per Subject / Usable amount of drug per tube = 403.2 g / 90 g = 4.48
= rounds up to 5

In this example, a kit containing fewer than 5 tubes per subject will be insufficient; yet a percentage of individual subjects will in fact consume the entire kit and require more, whether due to excessive application, loss of material, or shear treatment area. The science is in determining how to correctly peg the optimal kit size for the select percentage of potential subjects inside the targeted bell curve without incurring unnecessary expense, delays or forced dropouts.



Loss, Damage Assumptions

Loose units and additional kits also need to be estimated to address anticipated accidental damage during packaging and transportation to the pharmaceutical depot and then to clinical sites, in addition to loss and damage by sites and study subjects after distribution. Predicting the incidence of these particular variables tends to be a little trickier than many of the others. The optimal damage/loss percentages can be derived by using historical data, along with the experience and expertise of the CMO, logistics provider, CRO, PI and the study team.

More importantly, qualified CROs routinely implement procedures to ensure flawless distribution of drugs with little or no damage or loss. Ensuring reliable temperature controlled courier service and generally superior logistics optimizes this stage of the process. Proper guidance to sites and subjects regarding storage of their supplies are examples of areas where experienced clinical trial management can provide greater assurances.

FDA Drug Retention

A specific number of blocks must be retained at each clinical site at all times in order for the FDA to conduct necessary testing and inspection. “Retains” requirements increase the amount of RLD needed. Increasing the number of sites used in a CE topical trial correspondingly increases the amount of RLD to be accounted for as retains at each of those sites. The potential for block and kit retains to include damaged materials necessitates additional loose units reserved as retains.

The Code of Federal Regulations requires Sponsors and/or CROs to retain reserve samples of the investigational drug product for which the applicant is seeking approval (test article) and of the reference standard used to perform an in vivo bioavailability and bioequivalence study (12 CFR 320.38 and 320.63). The required number of reserve samples is laid out in the CFR as follows:

Each reserve sample shall consist of a sufficient quantity to permit FDA to perform five times all of the release tests required in the application or supplemental application. [12 CFR 320.38 (c)]

The details of quantities of reserve samples and sampling techniques in various study settings are provided in the FDA Guidance for Industry “Handling and Retention of BA and BE Testing Samples” (2004). The guidance gives an example of packaging and random selection plan for a blinded, multisite study of a dermatological cream product involving a SMO;

"The study enrolls 300 subjects with approximately 60 subjects at five testing facilities. The five times quantity for the test article and reference standard is 50 tubes for each product. In preparation for conducting the study, the SMO prepares 200 boxes that contain one code-labeled tube of test article and one code-labeled tube of reference standard in each box. The SMO randomly distributes 40 boxes to each clinical testing facility. The clinical facility randomly selects 30 of the boxes to dose 60 subjects.

The remaining 10 boxes serve as the reserve samples. In this example, staff (e.g., a pharmacist) not involved with the study may be recommended to ensure the study remains blinded. This packaging system ensures that an equal number of test article and reference standard are administered to the subjects at each site, and that an equal number of test article and reference standard will be maintained as reserve samples. Since 10 boxes are kept at each of 5 testing facilities, 50 tubes each of test article and reference standard are retained and the five times quantity reserve sample requirement is met. In addition, the requirement of random selection by each testing facility is also met. (p. 8)

Gross Total Number of Treatment Blocks

When we combine the number of blocks for retains with the number of treatment blocks previously calculated from the clinical sites along with the randomization factor and retain requirements we arrive at the total number of blocks. Factoring in any anticipated loss, damage and spoilage will yield the Gross Total Number of Blocks. In the final phase of this schematic, simple math produces the Total RDL Kits to be assembled and the Total Number of RDL Units that need to be purchased for an optimized trial.

Conclusion

Contract Research Organizations know first-hand that there are countless details to consider when planning a fully optimized study. Optimizing the amount of RLD and the corresponding budget associated with procurement is but one critical element to be considered. Even as we dissect this aspect of a fully optimized clinical trial, we uncover a multitude of other impactful dynamics that warrant further discussion and analysis. Some of these are sure to be addressed in greater detail in future white papers from bioRASI.

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