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

Clinical Endpoint ANDA Program Optimization
White Paper Series

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Introduction

Clinical trials present a variety of challenging economic issues. While most ANDA Sponsors invest time and money to set up clinical trials, rarely do they pay much attention to the cost of investigational materials. But when generic drug developers move from single dose BE/PK studies to steady state or even further to Clinical Endpoint (CE) ANDA Programs, the situation changes dramatically.

The cost of investigational materials can be, and often is one of the major portions of CE ANDA clinical trial total cost. This is especially true when the cost of the Reference Listed Drug (RLD) is extremely high. Considering the fact that a reference treatment group is typically between 25% to 50% of the total study population, which often exceeds 1000 patients, Sponsors of CE ANDA trials can easily spend hundreds of thousands or more on the purchase of RLD alone. Accordingly, the ability to optimize this major cost can be an important component in creating overall program success and efficiency.

In this Whitepaper (Part I), we will present the key variables and factors in calculating the amount of investigational material, required for different ANDA programs. We will provide some simplified formulas you can use to roughly estimate of the amounts of RLD you need to purchase for ANDA studies.

In the future, we will publish the Part II of this Whitepaper where we will go into more detail calculations for the required RLD in what probably is the most complex and expensive situation in ANDA trials: semisolid formulations for CE dermatological studies.

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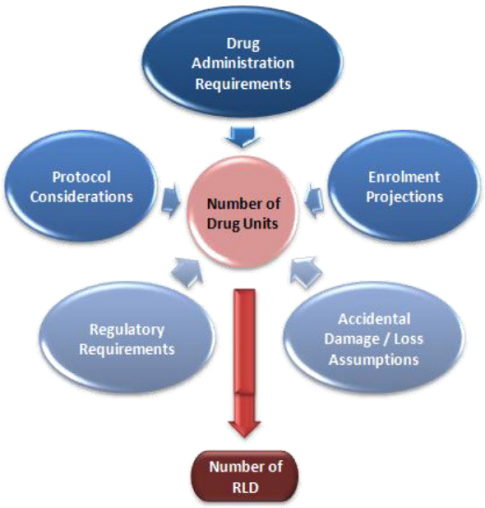
Variables and Considerations

Initially, determination of the RLD amount can be viewed as a modest task. After all, simple multiplication of several factors such as the number of study subjects, the number of drug units per subject (including assumptions for accidental damage/loss, the number of retains etc.) should be just enough to come up with the correct solution. However, such a simplification can often lead to either over or underestimation of the required amount of investigational drug. Both scenarios are undesirable and can put the overall study success at risk.

In order to determine the optimal amount of investigational material necessary to conduct a given clinical trial, there are a number of important factors that need to be considered. Accordingly, careful planning and analysis of these factors well in advance of the trial are key essentials for keeping costs of the investigational material as low as possible while ensuring the highest probability of the trial success.

In general, these factors can be combined in five main groups:

A. Regulatory Requirements
B. Protocol Considerations
C. Drug Administration requirements
D. Enrolment projections
E. Accidental Damage / Loss assumptions



Let's look deeper into each if these groups and the factors, considerations and assumptions that can help to optimize the amount of IM/RLD in ANDA studies.

Regulatory Requirements regarding Investigational Materials and the responsibilities of the parties involved with conducting clinical trials can be found in the following articles and guidance papers:

ICH GCP Part 4.6	Investigational Products
ICH GCP Part 4.7	Randomization Procedures and Unblinding
ICH GCP Part 5.13	Manufacturing, Packaging, Labeling and Coding of Investigational Products
ICH GCP Part 5.14	Supplying and Handling Investigational Products
21 CFR Part 312	Investigational New Drug Application, Subpart D – Responsibilities of Sponsors and Investigators
	§ 312.57 Recordkeeping and record retention
	§ 312.59 Disposition of unused supply of investigational drug
	§ 312.61 Control of the investigational drug
	§ 312.62 Investigator recordkeeping and retention
21 CFR Part 211	Current Good Manufacturing Practice in Manufacturing, Processing, Packing or Holding of Drugs
	Subpart H - Holding and Distribution
	Subpart I – Laboratory Controls
	Subpart K – Returned and Salvaged Drug Products
21 CFR Part 320.38	Retention of Bioavailability Samples
FDA Guidance	Handling and Retention of BA and BE Testing Samples

For the purposes of calculating the amount of investigational material, it is important to emphasize that (as per ICH GCP) it is the study Sponsor who is ultimately responsible for supplying investigators and investigative sites with the investigational product (section 5.15.1). According to the ICH GCP, the Sponsors shall (sections 5.15.4. and 5.14.5):

- ensure timely delivery of investigational products;
- maintain sufficient quantities of the investigational product used in the trials to reconfirm specifications;
- maintain records of batch sample analyses and characteristics.

Furthermore, the Code of Federal Regulations requires Sponsors and 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).

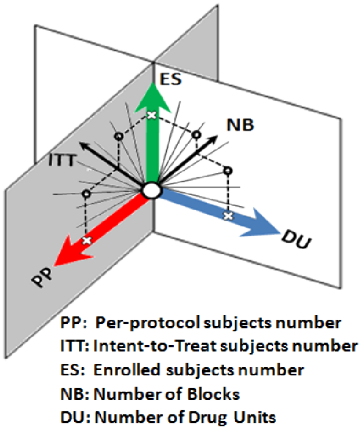
The details of quantities of reserve samples and sampling techniques in various study settings are provided in the FDA Guidance for Industry "Handling and Retention of BA and BE Testing Samples" (May 2004).

Protocol Considerations. Typical Clinical Protocols supply the following numbers and need to be strictly adhered to by Investigators:

- Number of Subjects
  - o Enrolle
  - o Evaluable Intent-to-treat (eITT)
  - o Per-Protocol (PP)
- Drug Administration Regimen
- Treatment Groups Ratio or Randomization Factor
- Number of Patient Kits per Block
- Number of Retained Blocks per shipment / per site

The number of study subjects and Drug Administration Regimen are key factors in calculating the amount of investigational material for the study. In clinical equivalence trials, the number of enrolled (or randomized) subjects depends on the required number of Intent To Treat (ITT) subjects for superiority comparisons and Per Protocol (PP) subjects in establishing bioequivalence. Subject number calculations are presented in detail in the comprehensive White Paper #10-10 "Patient Numbers Required in Clinical Equivalence Trials" by bioRASI, October 2010.

The number of PP subjects is estimated by biostatisticians and the study design team based on available regulatory and scientific data. The estimate of the proportion of ITT subject number (or slightly-restricted modified ITT (mITT) subjects) expected to qualify for inclusion into PP population, is estimated by the clinician together with an experienced CRO. Similarly, estimates of how many subjects needed to enroll in order to get sufficient number of ITT/mITT is the other variable that needs to be considered, and is based on certain assumptions in dropout rates and the level of confidence in projections provided by clinical sites and potential investigators of planned study. Both projected dropout rates from enrolled subjects (ES) to ITT and from ITT to PP represent one of the significant optimization paths in reducing IM and RLD cost (see following diagram).



The Randomization Factor (RF) or the ratio between treatment groups (e.g. Test: Reference: Placebo) is critical for determining the number of individual patients kits and subsequently the number of individual drug units per block.

Drug Administration Requirements come from the drug indication information that is part of the approved package insert for the reference drug to be used in the study. Additional information on the amount of drug to be administered can also be found in scientific articles as well as in the Summary Base of Approvals (SBA) for the reference product. The relevant factors here are:

- Treatment regimen and duration
- Number of administrations per subject
- Total number of Drug Units per subject
- Body surface (for topical)

Although treatment regimen and duration, and subsequent number of drug administration per subject are seen as predetermined based on the strict prescribing requirements, the correct total amount of drug units per subject might slightly change depend on certain assumptions such as required and projected windows for subject visits, body size and surface area (for topical drugs) etc.

For example, in some dermatological trials, the body area affected by the disease can vary significantly from subject to subject. Accordingly, the amount of investigational topical drug product usage is hard to estimate without extensive knowledge of the indication, disease severity and study population distribution in the geographical area of trial site location(s).

Enrolment Projections depend primarily on the Sponsor's and CRO's ability to determine the number of clinical sites as well as their performance level. The significant variables include:

- Number of countries
- Number of sites
- Enrollment projections per each site
- Number of shipments per each site
- Predicted dropout rate (from enrolled to eITT)
- Predicted dropout rate (from ITT to PP)

In the case of multi-center studies, the initial estimates for IM/RLD amount based upon high level assumptions have to be further refined by taking into consideration specific issues that could influence number of shipments, such as the number of sites, and their distribution in different countries. Involvement of more sites would proportionally increase the number of IM accounted for retains at the sites. Increases in numbers of sites will also increase the possibility of wasting extra amounts of drug as a consequence of magnifying projection errors from multiple sites.

On the other hand, the impact of these factors will be diminished by extensive site experience as well as excellent CRO practices during the site feasibility and the trial management processes. Decisions about choosing optimal set of countries and sites along with accurate analysis of recruitment projections and subject dropout rates, all are key success factors in optimization.

Accidental Damage / Loss assumptions include:

- Average Percent of Loss by subject
- Damage during packaging and logistics

Accidental IM damage during packaging and transportation to the depot and then to clinical sites, as well as loss and damage by study subjects represents another important area for IM/RLD optimization. Predicting these particular variables tends to be a little trickier than many of the others. The optimal damage/loss percentages can be chosen by using historical data, the experience and expertise of the packager, logistics provider, CRO, PI and the study team.

Possible Scenarios

As described above, the calculation process includes many variables and assumptions and presumes very complex pathways for determining the optimal amount of Investigational Material. A thorough discussion of, as well as defining a distinct optimization path for each of the elements of this puzzle is an important task. Moreover, we must consider and conduct a collective multi-factorial analysis in order to reach a successful determination. This process can be accomplished by a variety of statistical tools and simulation models. Such models are aimed at providing accurate results by combining analyses of the multiple assumptions and risk factors involved in the process. The details of some simulation models will be presented in future White Papers in this series.

For the purposes of the current Paper, we are presenting here a simplified approach for different types of commonly encountered scenarios, each of which takes different variables and assumptions into consideration for a rough estimate of the required IM/RLD, as shown in Table 1 below.

The scenarios denoted as 1 – 6 are:

1. A Typical Single Dose BE/PK Study
2. A Steady State BE/PK Study with Fixed Doses
3. A Steady State BE/PK Study with Variable Dosages
4. Multicenter Studies
5. Multicenter Studies Including Placebo and Packaging
6. Multicenter Studies Using Topical Creams/ Ointments/Gels

Table 1. Determination of amount of required drug in different types of ANDA clinical trials

Scenario 1	Equation	Variables	
A Typical Single Dose BE/PK Study	$A_d = [N_p * N_d] \times [(100+A_{ld})/100]+R_s$	N_p=const N_s=1 N_t=1 N_d=const	E_s=const (100%) R_s=const S_s = 1 A_{ld}=const (%)
Scenario 2:	**Equation**	**Variables**	
A Steady State BE/PK Study with Fixed Doses	$A_d = [N_p * N_t * N_d] \times [(100+A_{ld})/100]+R_s$	N_p=const N_s=1 N_t= const (multiple) N_d=const	E_s=const (100%) R_s=const S_s = 1 A_{ld}=const (%)
Scenario 3	**Equation**	**Variables**	
A Steady State BE/PK Study with Various Dosages	$A_d = [N_p * N_t * N_{dmax}] \times [(100+A_{ld})/100]+R_s$	N_p=const N_s=1 N_t= const (multiple) N_d=variable N_{dmax}=const	E_s=const (100%) R_s=const S_s = 1 A_{ld}=const (%)
Scenario 4	**Equation**	**Variables**	
Multicenter Studies	$A_d = [(E_s * N_t * N_{dmax}) \times (100+Ald)/100+Rs] \times Ns \times Ss$	N_p=const N_s=const (multiple) N_t= const (multiple) N_d=variable N_{dmax}=const	$E_s = N_p/N_s + N_p/4N_s$ R_s=const S_s = 2 (max) A_{ld}=const (%)
Scenario 5	**Equation**	**Variables**	
Multicenter Studies Including Placebo and Packaging	$A_d = P_{sh} \times N_s \times S_s$	N_p=const N_s=const (multiple) N_t= const (multiple) N_d=variable N_{dmax}=const $E_s = N_p/N_s + N_p/4N_s$	R_s=const S_s = 2 (max) A_{ld}=const (%) D_p=const $P_S = N_{dmax}/D_p$ $P_{sh}=E_S*P_S+R_S+A_{ld}$
Scenario 6	**Equation**	**Variables**	
Multicenter Studies Using Topical Formulations	$A_d = P_{sh} \times N_s \times S_s$	N_p=const N_s=const (multiple) N_t= const (multiple) U_d=const (%) A_b=const A_a=const $N_d = A_b * A_a * U_d * N_t$	$E_s = N_p/N_s + N_p/4N_s$ R_s=const S_s = 2 (max) A_{ld}=const (%) D_p=const $P_S = N_d/D_p$ $P_{sh}=E_S*P_S+R_S+A_{ld}$

Where: A_d = Amount of Required Drug; N_P = Number of enrolled patients; N_S = Number of Sites; N_t = Number of Treatments; U_d = Unrecoverable amount of drug in drug unit (tube, vial, etc) (%); A_b = Affected body surface (max); A_a = Amount of drug per application; N_d = Number of Drug Units per Subject; N_{dmax} = Max Number of Drug per Subject; E_s = Enrolment per site; R_s = Retention Samples; S_s = Number of Shipment; A_{ld} = Accidental Loss/Damage; D_p = Drug units per package; P_s = Packages per subject; P_{sh} = Packages per shipment

These scenarios cover a wide range of ANDA trials extending from a simple Single-Dose, Single-Site pharmacokinetic study through complex Multi-Dose, Multi-Center dermatological studies. The equations presented reflect assumptions and considerations specific to each type of study.

Looking Forward

Sponsors of clinical trials invest time and money to set up clinical sites, recruit patients, and manage studies. One of the largest cost components involves the purchase of Investigational Materials, more specifically the RLD under study. The use of simple calculations to predict the amount of drug required for the trial can lead to either increased costs and waste by purchasing too much or affect schedules adversely and therefore time to market by purchasing too little.

We have presented a methodology for determining the optimum amounts of RLD that take more of the real-life, real-world variables and assumptions into account and shown how it functions in six scenarios ranging from simple to complex. We will be presenting further details of the most complex and often most expensive scenario #6 in the Part II of this White Paper and will address some simulation models and approaches we use in future Papers.

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