DEVELOPMENT OF AN EXPERT SYSTEM FOR TROUBLESHOOTING FLOW PROBLEM

A THESISSUBMITTED TOTHEGRADUATE SCHOOLOFHEALTH SCIENCES OF NEAR EAST UNIVERSITY

By
FAISAL MAHYOUB FARHAN

In Partial Fulfillment of the Requirements for The Degree of Master of Science in Pharmaceutical Technology

NICOSIA, 2018

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I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

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ACKNOWLEDGEMENTS

An endless thanks to Allah for blessings, since I was a child, I have been dreaming to be a pharmaceutical professor. Now Alhamdulillah, I achieved one of my aims by finishing the Master degree in order to accomplish the great dream.

During this journey of my thesis, I would like to thank whoever:

My mother and my father whom always support me that I cannot recompense them whatever I do. I am always going to pray for them to be safe and healthy.

I would sincerely like to thank my academic inspiration, my advisor **Assist. Prof.Dr. Metin Çelik** for his academic guidance and helping me from start. He always considers me as his son, and as a close friend. It was a real privilege and an honor for me to share his exceptional scientific knowledge and extraordinary human quality.

I would also like to extend my warm thanks to my co-advisor and the head of the Pharmaceutical Technology Department Asst. Prof. Dr. Yıldız Özalp.

In the last but not least, to my closer friends **Mohammed** and **Mazen**, I really express my gratitude for unconditional friendship, support, patient throughout this journey. I am lucky to know you.

ABSTRACT

Several pharmaceutical processes, such as blending, transfer, storage, feeding, compaction, involve powder handling, in other words, powder flow. The flow of powder during manufacturing dictates the quality of the product in terms of its weight and content uniformity. Unfortunately, the science of powder blending, and powder handling often is not generally well understood by those who formulate products or select processing equipment. Therefore, some processes that are prone to problems with blending, segregation, and flow have been developed and introduced into production, ultimately resulting in varying degrees of content uniformity issues. This problem is further complicated by the difficulties encountered in physically sampling a stationary powder bed using sample thieves, which have been demonstrated to be very prone to sampling error. The result of this error is samples that do not represent the state of the blend from where they were collected, which may lead to erroneous conclusions about the true uniformity of the powder blend. There may be a number of root causes for a given flow problem, therefore, trouble-shooting a flow problem can be highly complicated process. This is where use of artificial intelligence, namely an expert system which is a computer program capable of making recommendations or decisions based on knowledge gathered from experts in the field, could be very useful. In this work several dozens of decision trees, which make the foundation of rule-based systems were developed using the knowledge gathered from literature. Developing an easy-to-follow algorithm, decision trees were chained to pin point the root cause of a given flow problem. The possible solutions were ranked by a weighing factor to show the what could be the highly likely root cause of a problem. In the algorithm, most of the problems and possible root causes of the flow related problems were presented.

Key Words: Expert System, Flow, Flow Problems, Decision tree.

ÖZET

Karıştırma, aktarma, depolama, besleme, sıkıştırma gibi çeşitli farmasötik işlemlertoz işleme, diğer bir deyişle toz akışıyla yakından etkilenir. Üretim sırasında tozun akışı, ürünün kalitesi ve içeriği bütünlüğü açısından kalitesini belirler. Ne yazık ki, toz karıştırma ve toz akışı bilimi, genellikle ürünleri formüle eden veya prosess ekipmanını seçenler tarafından iyi anlaşılmamaktadır. Bu nedenle, karıştırma, segregasyon ve akış problemlerine eğilimli bazı yaklaşımlar geliştirildi ve üretime dahil edildi, ve bu, sonuçta değişen derecelerde içerik homojenliği sorunlarına yol açtı. Bu problem, numune alma hatasına çok eğilimli olduğu kanıtlanmış örnek numune alıcılar kullanılarak sabit bir toz yatağının fiziksel olarak örneklenmesinde karşılaşılan zorluklarla daha da karmaşıklaşmaktadır. Bu hatanın sonucu, karışımın durumunu temsil etmeyen numunelerdir, bu da toz karışımın temsili hakkında hatalı sonuçlara yol açabilir. Belirli bir akış problemi için birtakım kök nedenler olabilir, bu nedenle, bir akış problemindeki sorunu giderme oldukça karmaşık olabilir. Yapay zekanın, yani alanında uzmanlardan toplanan bilgilere dayanarak tavsiyede bulunabilecek veya kararlar verebilen bir bilgisayar programı olan uzman bir sistemin kullanılması çok yararlı olabilir. Bu çalışmada, kuramsal sistemlerin temelini oluşturan düzinelerce karar ağacı, literatürden elde edilen bilgiler kullanılarak geliştirilmiştir. Takip edilmesi kolay bir algoritma geliştirmek için, karar ağaçları belirli bir akış probleminin temel nedenini gösterecek şekilde zincirlenmiştir. Olası çözümler, bir problemin büyük olasılıkla muhtemel sebebinin ne olabileceğini göstermek için bir ağırlık faktörü ile sıralandı. Algoritmada, problemlerin çoğu ve akışla ilgili problemlerin olası nedenleri sunulmuştur.

Anahtar Kelimeler: Uzman Sistemler, Akış, Akış Problemleri, Karar Ağaçları.

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LIST OF ABBREVIATIONS

FT4: Powder Rheometer.

PTG-S4: Powder Characterization Instrument.

ASTM: American Society for Testing and Materials.

RSD: Relative Standard Deviation.

QC: Quality Control.

AOR: Angle of Repose.

USP: United States Pharmacopeia.

V0: Unsettled Apparent Volume.

Vf: Final Tapped Volume.

ρbulk: Bulk Density.

ρtapped: Tapped Density.

REF.: Reference.

ES: Expert System.

CHAPTER ONE

INTRODUCTION

1.1 Powder Flowability

Powder flowability is the ability of a powder to flow in a desired manner in a specific piece of equipment. Flow of powders may be: Free-flowing or non-flowing(cohesive). The flow affecting on the manufacturing of tablets, capsules, filling of powder in container involves several powders handling steps, including blending, transfer, storage, and feeding to a press or a dosator. The inability to achieve reliable powder flow during these steps can have a significant adverse effect on the manufacture and release of a product to market. Two flow patterns developed when powder flow from container, the first one is the funnel flow, the second one is the mass flow. In funnel flow, the side wall materials stagnant whereas flow of funnel-shaped material take place, First-in-last-out, chance of segregation and suitable only for free-flowing powder. In mass flow, all of the material is in motion, First-in-first-out, minimize segregation and preventing ratholing. The most common powder flow problems are; Ratholing, arching and flooding. To prevent these problems we must, increasing the outlet diameter, reducing the filling height of powder, reducing the equipment capacity, reducing the cohesive strength of powder and utilizing the mechanical assistance.

To measure the flow properties, we have certain tests:

1- Angle of repose: the internal angle between the surface of the pile and the horizontal surface. And it depends upon, the density, surface area, shape of the particles and the coefficient of friction of the material. This angle is in the range 0-90. It used interparticulate friction or resistance to movement between particles.

2- Carr’s compressibility index and Hausner ratio: both are determined by measuring the bulk volume and the tapped volume of the powder.

3- Flow through an orifice: useful only for free-flowing materials. We have a guideline for the dimensions of the cylinder.

4- Shear cell method: the force necessary to shear the powder bed by moving the upper ring is determined. There are three types of the shear cell methods, cylindrical, annular and plate-type shear cell.

5- Cohesion index: a low cohesion index is associated with non-cohesive free-flowing powders.

6- FT4 powder rheometer: the forces causing the deformation and flow is measured.

7- PTG-S4 powder characterization instrument: it can measure the flow time, cone angle and the flowability.

8- Penetrometery: the pressure of penetration in Pascal was used to estimate flow rate. It used for non-consolidated pharmaceutical powder excipients for example, sodium chloride or boric acid.

Therefore, we can control powder flow by using, Mucon iris diaphragm valve, Powry valve, vacuum assisted powder flow nozzle, Funken continuous auto feeder and fluidizing hopper flow control valve.

The powder flow is very important in pharmacy:

1- Tablet manufacturing.
2- Capsule manufacturing.
3- During drug delivery.
4- During mixing and sieving.
5- During unloading of packs.
6- During transportation through conveyers.
7- During filling of powders, dry suspension and dry syrup.

1.2 Search Tree Structure or (Decision Tree)

Related with inferencing is the search mechanism. In several cases it is possible to characterize the knowledge base using some kind of search tree structure or (decision tree). Inferencing then construe into a problem of searching a tree to reach to an effective solution. A special language has been developed to represent a decision tree. The root node is the initial state node and it is from which other nodes are connected via branches. Nodes with no sequence are called the leaf nodes and designate the end of the tree. The nodes are split into different levels characterizing the depth of the tree. The root node is often designated level 0 and successive deeper levels are designated via sequentially higher numbers (Figure 3.3). There are two strategies commonly used to search such a tree:

- Depth-first search: in which a search is initiated downward along a given route until a solution or dead end is reached. In the final case the process backtracks to the first alternative branch and tries it. The procedure is repeated until a solution is found as shown in (Figure 1.1a).
- Breadth-first search: in which a search is initiated at a specific level on each branch in turn before moving on to a different level as shown in (Figure 1.1b).

A depth-first search guarantees a solution but might take a longer time. It is especially useful where branches are short Breadth-first search routines are useful while the number of branches is relatively small and while the numbers of levels in each branch different. Finally, the last and most important component of an expert system is its knowledge base where all the knowledge concerning the domain is stored. The discipline whereby this knowledge is acquired from the experts, structured and represented within the knowledge base is known as knowledge engineering.

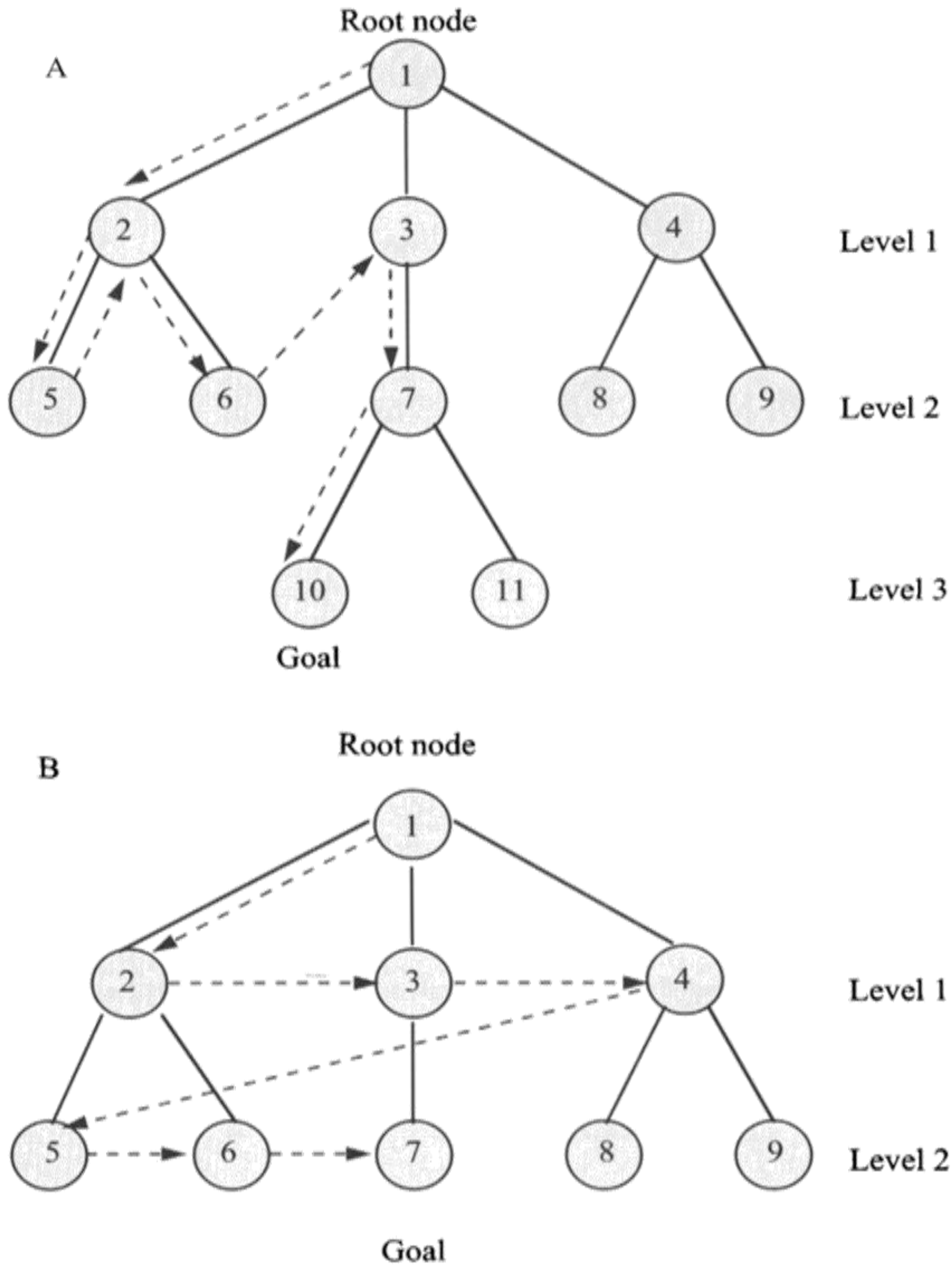


Figure 1.1: Search trees: (A) Depth-first search; (B) Breadth-first search.

1.3 Contributions of the Research

In the above description, the decision tree is the parameter for the prediction of the blend uniformity.

This project is utilized to make another approach. Decision tree, for the prediction of the blend uniformity problems and the evaluation of the parameters for the contribution on powder blending. The information was collected by experimental and theoretical model.

The investigations presented in this thesis prove that the Decision Tree can predict the problems of the blend uniformity.

The specific objective of this assignment is to create an expert system to predict and solve the blend uniformity problems.

1.4 Outline of Thesis

In this chapter, the introduction of flowability and search tree structureswere presented. Overview of powder flowability including the definitions and the effect of it on the pharmaceutical industry, handling, storage and the basic methods to test the powder flow wereprovided in Chapter 2. In Chapter 3, the expert systems definitions, features, knowledge acquisition and the applications of expert systems were reviewed. Expert systems componentswere also discussed in this chapter. Finally, the materials and methods, results and discussion and conclusion were presented in Chapters 4, 5 and 6, respectively.

CHAPTER TWO

LITERATURE REVIEW

2.1 Introduction

Powder flowability is one of the important parameters in the pharmaceutical tableting process. The flowability is affected by both the particles properties and the tableting equipment characteristics. Although it is generally accepted that powder flowability increases with an increase in particle size, quantitative studies and comprehensive theoretical insights into the particle property effects are still lacking. Therefore, powder flow is a key requirement for pharmaceutical manufacturing process. Tablets are often manufactured on a rotary multi-station tablet press by filling the tablet die with powders or granules based on volume. Thus, the flow of powder from the hopper into the dies often determines weight, hardness, and content uniformity of tablets. In case of capsules manufacturing, similar volume filling of powders or granules is widely used. Understanding of powder flow is also crucial during mixing, packaging, and transportation. And thus, it becomes essential to measure the flow properties of these materials prior to tableting or capsule filling.

2.2 Flowability Definition

An easy definition of powder flowability is the ability of a powder to flow. But with this definition, flowability is sometimes thought of as one-dimensional characteristic of a powder, wherever the powders can be classified on a sliding scale from free-flowing to non-flowing. This simple view it makes a lack on the science because if we ask whoever works with powders, whether in the laboratory or in the production, quickly they will know and recognize that powder flow is complex. The flow has multidimensional behavior and it depends on the characteristics of the power. This is why the quantification of flow is considered to be difficult.

To collect these multivariable problems, some propose that all test values be considered and others suggest that those values can be factored into a single flowability index. We cannot express the flowability in a single value or index. In fact, flowability is not an inherent material property at all. Flowability is the result of combination of powder physical properties that affect powder flow and the equipment used for handling that powder, storing, or processing the powder. Same consideration must be given to the powder characteristic and the equipment. The same powder may have good flow in one hopper but poor in another. Otherwise, a given hopper may handle somepowder well, but itcauses hang up to another powder. This is why a more accurate definition of powder flowability is the ability of powder to flow in a desired manner in specific equipment. This definition is more accurate because the free-flowing term becomes meaningless unless the specific equipment handling the material is specified. The specific bulk characteristics and properties of powder that affect flow and that can in principle be measured are known as flow properties. Example of flow properties includes density (compressibility), cohesive strength, and wall friction (Rumpfand Herrmann, 1970).

2.3 Flowability Effects on Pharmaceutical Industry

The flowability is a factor that can affect direct or indirect on the pharmaceutical industry processes such as (powder transfer, powder storage, blending, compaction processes, fluidization and separation of the small quantity of powder from the bulk) (Podczeck, 1998). And also, the poor flow can have many implications including (limit live capacity, segregation of fines or dusts, idle equipment or process, erratic or stop flow, powder flooding or flushing, structure vibrations or quacking, missed shipments or delays, caking, agglomeration and wasted materials). All these problems occurr when the power flow is poor, and it will have a serious effect on the industrial production.

2.4 Powder Transfer

The effect of flowability on the powder transfer it can be happened when a raw material or in-process powder or product is in bulk form, it should be transfer between the equipment for storage, transportation, or processing. These transfers driven by gravity and involve dropping product from a blender or portable container, bin, silo, or drum by opening a valve. These steps including a large number of powders with a large number of contacts between the powder particles and these contacts may be changing continuously. The size of the equipment involved for example, the transfer chutes (if used). Many problems can occur as power flow through the equipment. If the powder has a cohesive strength, an arch or rathole may form. An arch is a stable obstruction that forms within the hopper section generally near the bin outlet. The arch supports the rest of the bin's contents and preventing discharge of the remaining powder. A rathole is a stable pipe or vertical cavity that empties above the bin outlet as shown in (Figure 2.1).

Figure 2.1: An example of ratholing.

Erratic flow may be happened and it is the result of an obstruction alternating between an arch anda rathole. Other flow problems related to the state of aeration or density of the powder discharge. When especially fine powders discharged it may create flooding. How does the flooding happen? When a rathole collapse, the falling particles pull air and fluidized. If the powder-handling equipment cannot handle liquids, powder will flood through the system with no control. Even if the powder is contained, its bulk density can undergo considerable variations if fluidized, and it will have a negative effect to down-stream equipment. Therefore, the flow-rate limitations also may show when fine powders are handled. The expansion of voids during flow can create upward air pressure gradients at the outlet of discharge equipment. During discharge, this gradient acting against gravity reduces or limited the discharge rate. These flow problems are strongly affected by the flow pattern of a powder during discharge. There are two flow patterns: funnel flow (core flow) and mass flow as seen in (Figure 2.2).

- **In funnel flow**, active flow channel forms above the outlet with non-flowing powder at the sides and It called first in-last out flow sequence. When the level of power decreases, the layers of non-flowing powder may or may not slide into the channel, sometimes it is resulting in the formation of a stable rathole. In addition, funnel flow can increase the extent to which the segregation affects the discharging powder.

- **In mass flow**, all the powder particles moving together whenever any is withdrawn. Powder from the outlet as well as from the sides moves toward the outlet. And the mass flow provides a first in-first out flow sequence, and also provides a steady discharge with consistent bulk density, and yields a flow that a uniform and well controlled. And mass flow also reduces some types of segregation of powder. Because all the material is moving, velocity profile still exist within the hopper. To achieve the mass flow there are some requirements includes sizing the outlet large enough to prevent forming an arch and ensuring that the hopper walls already smooth enough to promote flow along them.

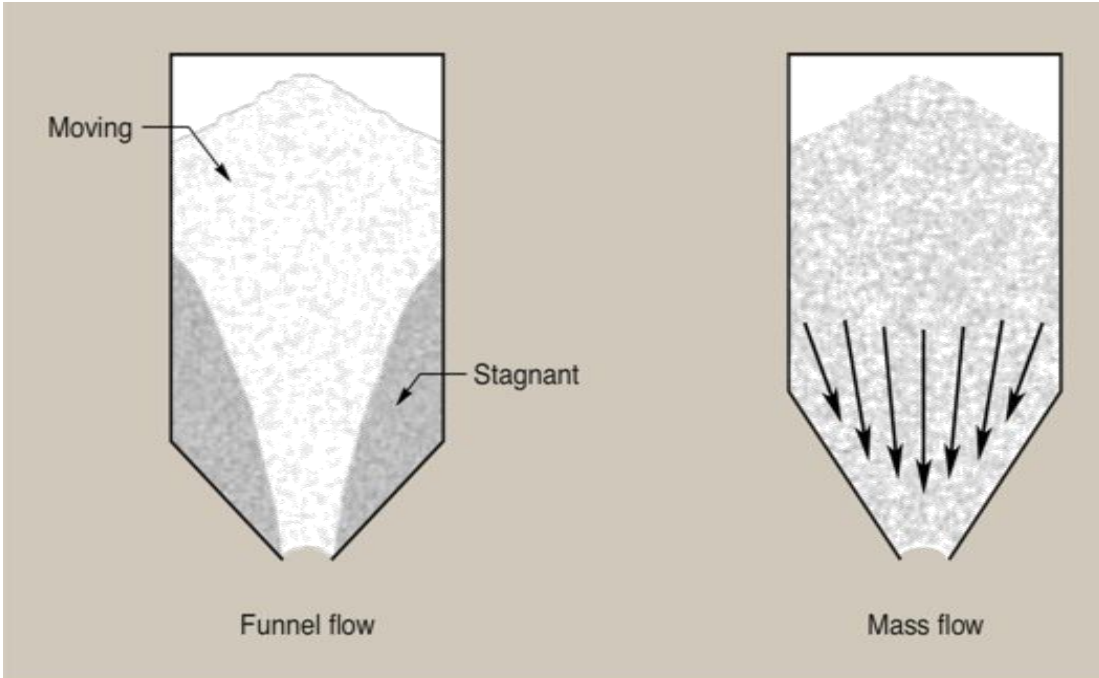


Figure 2.2: Examples of funnel flow and mass flow patterns.

The properties of the powder are based on a continuum theory of powder behavior and it can be described as a gross phenomenon, Abandoning the interaction of individual particles. This theory has been proven over the past 40 years in thousands of installations handling the full spectrum of powders used in industry (Carson andMarinelli, 1994).

2.5 Powder Storage

Through processing, immediate transfer and consumption of a powder are not always possible or desired because of the need for analysis, equipment availability, or transporting between facilities and companies. In these cases, bulk material is saved in a container. As in the case of following material, particles are in contact with each other. However, these contacts do not change continuously. Prolonged contact, in conjunction with moisture and pressure from the weight of material above, may change the bonds between particles as well as the particles may change ether moisture crystallization, or reactions that absorb or emit heat may lead to dramatic increasing in cohesive strength, agglomeration of smaller particles into larger ones, or caking. External forces such as vibration induced during transportation or storing (stacking of containers that deform) aggravate these effects. Expansion and contraction results of temperature changes also can significantly participate to increase consolidation. All of those factors can make a problem by itself, but if happened together the factors will make the problems further. As a result of these conditions, an increase of cohesive strength can produce discharge from the container very difficult or impossible because of the problems caused by arching or ratholing. If the stronger bonds lead to caking, the material will not be usable at all. The possibility for this time depending effects to occur can be examined by measuring the increasing in cohesive strength of the powder after time at rest. The direct shear teaser is a procedure in which a vertical load can be applied and support for a specific time (ASTM, 2016). External influence such as humidity or temperature can be applied during these tests. After the specific time has passed, a horizontal shearing force is applied and calculated. The correlation between the cohesive strength and the powder as a function of the consolidating pressure after storage at rest then is developed (Jenike, 1980). This new time depending flow function can be analyzed to specify the minimum outlet diameters of converging geometries to stop arching and ratholing. A comparison with continuous flow test results will display what strength the powder has increased and what changes in equipment geometry are needed to overcome these gains. Conversely, the tests may display that, after certain given time and set of external effects, it is not expected that the material will flow under the gravity alone. In the other hand, there is an important valuable insight into the storage requirements for a powder and environmental controls or special handling are needed to avert potential problems.

2.6 Separation a Small Quantity of Powder from The Bulk

In the pharmaceutical process including powder handling, in some point a small quantity of powder must be separated from a larger blend or mass of powder, e.g., when producing tablets or filling vials. The solid dosage forms weighing less than a gram usually are produced from a batch approximately larger than 1000 kg. Ideally, each of these dosage forms is identical in weight and composition. For most systems in specific for automated, high-speed systems consistent powder flow at this point in the process is essential to supply consistent weight of individual doses. Because of poor powder flow, a slow-speed process that works good may not work at all when the rates are increased. Wherefore, at higher speeds, a constant feed rate and a consistent bulk density of the powder are desired. IN several of these operations, particles are obliged into a die cavity or vial (orifice). If the powder has enough fluidity, gravity alone can immediately fill the orifice. A combination of methods also can be used. With equipment that makes an individual dose, the orifices are usually small, typically less than 0.25 in. Manufacturers usually use mechanical assistance in the form of paddle feeders, wipers, doctor blades, or agitator arms. These devices oblige the powder into the cavity and/or aerate the powder so it acts more like a liquid and less like a powder. Complicating the flow behavior — and accidentally, complicating the analysis — is the typical presence of significant ambient vibration that is inherited to the powder and, depending on how and where it is applied, may support or prevent flow.

Another variable that should be considered is the effect of (Triboelectric effect), or building of a static charge, formed by the fast flow of powder. This phenomenon is ephemeral and can be difficult to reproduce, identify, and quantify. So far triboelectrification can have an obvious effect on the interparticle forces that affect flow. Therefore, particle velocities are little high, and there is significant interparticle motion; that is contacts between particles are short lived. Indeed, as the powder becomes aerated, particle-to-particle contacts may not be sufficient to carry solids pressure, and the proposition that the powder can be treated as a contact bed fails.

Because of this behavior, and because of the small orifices and low solids pressures implicated, techniques used for hopper design cannot be used to predict flow. Although several operations mays considered, tableting is highly common and explains the principals involved. In tableting, the ability of the powder to flow into the small die is key to producing consistent tablet weights. This tendency is ruled by the ability of particles to separate from each other (low particle-to-particle cohesion) and the state of aeration of the powder. In this case, the state of aeration is ruled by another flow properties of the powder like permeability and compressibility, also the equipment that handles the powder (e.g., press-hopper shape) and handling history (e.g., storage time before compression and flow rate through the equipment). Otherwise, even if we know these parameters we cannot predict flow behavior during separation of the dose. Within the universe of tablet presses, the design and the operation of the feed frames used to meter powder to the die table can change from one to another. Between kind of press manufacturers, and even within a line of presses, they have different paddle diameters, heights, speeds, shapes, and also various numbers of paddles and blades. This led us to know that a powder can have differences in flow between equipment, simply because of the differences with the feed frame itself. For a specific design, control of the feed rate upon the die table is critical. If the rate is very slow, the dies will be starved. And if it is very fast, then the powder can deaerate and/or densify in an inconsistent manner before filling it. These Two situations drive to erratic tablet weights. Again, flowability is a function of the material being handled and the equipment used to handle the material.

As Shangraw states, “There are two basic approaches to increasing die feeding efficiency:

a) Force material into the die cavity.

b) Improve the flow properties of material directly above the die cavity so that the material will naturally flow downward.

The later approach appears to be more realistic and serves as the basis for most tablet machine modifications for improvement of die fill” (Shangraw, 1989). Note that as is usually the case, there is confusion with terminology in these statements. Flow properties cannot be modified without some chemical or physical change to the material (e.g., moisture or particle size). Flowability, also, can be increased by machine modifications, which could serve to aerate the material to let it to “naturally flow” and increase die filling. Because of the complication of powder flow through a feed frame, upon a table, and into dies, no first principles have been developed to clarify or model the flow behavior. The continuum model, which works well for powder flowing in a bin, is less descriptive of this process and unsuccessful to always predict the true flow behavior. Without a model or theory of how powder flows within a feed frame, it is impossible to apply any bench-scale test results to predict true performance. Experimental modeling is therefore required. Because of the complication of the problem, nothing less than an immediate full-scale test can describe the true flow behavior. Such tests can be inconvenient, expensive, or impossible. Unfortunately, in most cases, “The most effective way to measure the effectiveness of a glidant in a powder blend” (or other behavior) “is to compress the blend and define weight variation” (Peck et al, 1989).Full-scale tests have their obstacle, especially when the next new material or press is presented. To paraphrase Lippens, another problem with experimental approaches is the potential of a never-ending series of articles in which authors prove that their new empirical equations based on their own data predicts behavior better than an already published empirical relation (Lippens&Mulder, 1993).

This situation is a result of the nature of the multivariable problems of mixing different powders, test methods, and applications. Instead of theoretical models or detailed, complete, proven, experimental models to predict flow over a press feed frame, the industry depends on other tests as indicators. Traditional tests are Carr indices (ASTM, 2014), Hausner ratio (the ratio of tapped to loose-bulk density) minimum orifice diameter, Flow rate through a funnel and Shear cell and avalanche tests also are used. There is not of these small-scale tests simulate the state of aeration of the powder before the feed frame and the effects of the feed frame itself, these two have a significant effect on the arching tendency and the maximum flow rate of the powder. The problem is none of these tests give a physical parameter directly related to the flow at the press. Therefore, it is hoped that flow test result directs will correlate to tablet weight relative standard deviation (RSD), as could have been the case with a prior product or application. Perhaps, tests for minimum orifice diameter and flow rate through a funnel appear more applicable for predicting the maximum rate of compression because those measurements most be closely simulate the need to fill a small die fast enough as possible. Yet, rarely have published papers cited a strong connection between any of these flow properties and weight variations during a development of a dose. Nyquist discovered a correlation by relating shear cell data to tablet weight RSD and frequency of tablet machine adjustments (Nyquist, 1984).Because neither of these flow properties test results can surly predict flow behavior, the easiest test method usually is used without consideration to the significance of the results. This is similar to the story of that person who was looking for a lost wallet under the streetlight because the light is better, although the wallet was lost well away from the streetlight in the dark. Unfortunately, no one until now has a clear light on how to address powder flow properly on the press using first principles that can be quantified with a bench-scale tester. The capsule filling is another example of how flow properties can be used as a predictor. Unlike a tableting operation, a capsule filling operation requires the powder to have a proper strength to form a plug and rest in the dosage tube until the plug is ejected into the capsule shell. (These criteria can be specified based on wall friction and cohesive strength tests). Simultaneously, the remaining bed of powder must be sufficiently free flowing to breakdown to fill in the space that was created. Again, experimental approaches are often taken in which a correlation of flow behavior to some standard flow property test is desired. Other applications in which a unit dose is made and powder flow is a concern — outside of conventional tablets and capsules — include inhalers and electrostatic deposition of active drug upon tablets. These and other novel processes need new tools to make an investigation to the effect of flowability during the development of the unit dose.

2.7 Flow of Powder During Blending

Blending is achieved by a complex of three primary mechanisms: shear, convection, and diffusion (or dispersion). The extent to which each of these mechanisms occurs is a function of many variables. One group of variables relates to the equipment itself such as blender type and speed of blending. Another group of critical variables involves the flow properties of the powders being blended. For example, with the diffusion mechanism, particles move diffuse through a dilated or expanded bed of powder. The ability of the bed to dilate or spread and the ability of particles to migrate depend most onto the cohesive strength of the powder. Powders with small cohesive strength spread more easily. Thus, shorter blend times can be completed if the major component of the blend is more free-flowing. Further, if convection is considered, a moderate cohesive powder might blend faster because chaotic patterns are inserted see (Figure 2.3). Yet, free-flowing blends may segregate easily onto after handling, especially if the different powders of the blend do not adhere to each other. A better blend may be accomplished if the minor powder is somewhat cohesive or has a capability to adhere to the major powder of the blend. (This example is referred to as an ordered or adhesive blend). In addition, a better blend could be acquired and maintained if the blend is slightly cohesive compared with a blend that is free flowing (Chang et al., 1995).

Figure 2.3: Examples of (a) free-flowing and (b) weakly cohesive powder blends.

2.8 Fluidization

Fluidization includes airflow counter to the gravity force through a bed of powder. In a fluidized state, particles are easily separated from each other. Fluidized handling is of interest for many reasons: Some of the granulation processes depending on a fluidized bed for agitation and mixing to produce uniform particles. Fluidized feed systems can be used in applications in ether high material feed rates or very fine powders are involved. There are some features of these systems like it may include a permeable membrane or air injection points on a hopper surface. We can use a bed drying processes in this is also a feature, although the airflow rates are usually lower because complete fluidization may not be needed and, otherwise, it may need to be avoided and this is depending on the process requirements. Pneumatic conveying, in which an expanded bed of powder is transported by injected air within points, can be considered an extreme case of fluidized handling. The ability of air to separate the material particles depends on the flow properties of the powder. If a bed is allowed to expand, its bulk density will be less as the airflow through the powder high. Powder permeability is described as the ability of the air to move through a stationary bed, and that is a function of the bulk density. As the bed expand and reaches a minimum density, particles separation and movement will be relative to one another. At this point, defined as the minimum fluidization velocity, pressure decreases across the bed remains relatively constant as air velocity increases. Because of this information, the airflow requirements for a fluidizing process can be specified, and the supply system can be sized accordingly. And also, this information can be used when complete fluidization must be prevented. The ability of the particles to separate from one another is based on particle-to-particle bonding or cohesion. Cohesive powders might not fluidize easily and sometimes it gives as an opposite reaction and form large flow channels allowing air to channel past stagnant zones. Geldart developed connection describing the ease with which materials can be fluidized (Geldart, 1973). These relationships explain the dependency of mean particle diameter and particle density on general fluidization directions. Although, these are purely empirical correlations for relating material behavior directions to two particle properties. Cohesiveness is ignored. For example, addition of moisture to a dry powder leads to increasing the cohesiveness of the powder and reduces the ability to fluidize. In fact, because its particle size and density still the same, Geldart's chart cannot distinguish this behavior. Generally, depend on past connections might give us some guidance, but each new material will have a new correlation (Lippens&Mulder, 1993). After fluidized, powder flow may in principle be modeled as a non-Newtonian fluid. The settling or deaeration of powder might be as much important as the requirements for fluidizing it. Settling times are affected by the same properties that affect fluidizing potential. These properties involve the permeability of the bulk powder as well as the mean size and density of the particles. Fast settling times usually are desired to prevent flooding and segregation. Flooding can be a result when the retained air pressure inside a bed acts as a driving force if it is discharged from below, as in a bin or hopper. Segregation via air entrainment can be a result when the air trapped inside a material (example, during the filling of a bin from above) escapes upward and transfers with it more fine particles that are then deposited on the top surface. Deaeration behavior inside the bin (example, peak air pressure) can be calculated by having the permeability and compressibility of the powder as well as the in-feed rate and bin geometry. Those parameters also can be used to know the potential for flooding and segregation (Botterill&Bessant, 1973).

2.9 Flow Properties as Comparative, Physical Test Methods

In many examples, QC reviews should be accomplished on powders to define if certain characters of the powder fall within a predefined range. These characters involve chemical composition, particle size, color, moisture, and, usually flow properties. QC reviews can be done by a supplier before sending the raw materials, by technicians for process control, or by a user of incoming raw materials. The applicability of the flow properties tests it depends highly on the user for what is he trying to capture. For example, if someone is worried that a specific batch of material might arch when moved into a bin, a shear test might be the most overall QC test to behave. Knowing, whatever these QC reviews might hold up the shipment or speed further processing of the powder, faster test methods usually are needed. One option is abbreviated shear-cell testing. Other QC reviews involves angle of repose, compressibility, Carr indices, the Johanson indicizer, flow funnels, minimum orifice diameter, dynamic angle of repose, or the Jenike & Johanson QC tester (Schulze, 1996). Each flow property test may be used as a QC test, and usually the fastest and the most convenient test is chosen. This choice is acceptable, as long as the user knows of the test's restrictions. Because test methods such as angle of repose and flow funnels do not separate attributes of the powder, the convenience of a test and the acceptance limits should be experimental. Applying the results of this test depends on comprehensive testing or experience and judgment. In fact, many batches of acceptable product should be made (defining the acceptable limits on quality) over with many unacceptable batches. Knowing good and bad without flow properties tests is the difficult part. The QC flow properties tests methods should completely identify any case. Usually, various test methods will create different results, which is no surprise given the various physical mechanisms included with every test. Many studies have exhibit that for a group of materials, various test methods rank these materials differently with respect to flow (7 millions, and unpublished data from Jenike & Johanson, Inc.). With different rankings by every QC test, how does one apply the results? One time again, the application and equipment should be considered, and the test method most closely simulating the flow attitude in the actual process must be chosen.

2.10 Angle of Repose (AOR)

In response to the need in industry for a fast and reproducible method of calculating the flowability of powders in processes including transport and storage, the clearly simple idea of calculating angle of repose has been revived. The simple tester first used has developed over a number of years into the current version which is shown to be able of handling many small samples of powders that are even a little cohesive. There are considerable pieces of equipment and methods that are available and may be used to measure particle properties for example, particle size distribution (PSD), particle density and shape. Although, it is not yet possible to use basic particle properties such as these to foretell the attitude of bulk powders except in a generalized way, and particular test methods have to be used in order to get a reliable data that is able to use for designing equipment such as storage hoppers that will not block. It is quite agreed that there are two basic types of angle of repose, i.e. the static and dynamic angles. Although, there are at least eight methods of measuring the angles of repose, and every method will give somehow different values. However, the published values of the angle of repose are rarely comparable (Brown&Richards, 1970). In establishing a relationship between powders flowability and many simple physical measures, Carr (1965 & 1970) and Raymus (1985) suggested that angles of repose below 30^o indicate good flowability, 30^o-45^o some cohesiveness, 45^o-55^o true cohesiveness, and >55^o sluggish or very high cohesiveness and very limited flowability. Geldart et al. (1990) and Antequera et al. (1994) were more inclined to use the 40^o criteria, based on the data of Brown and Richards (1970), in classifying free-flowing and cohesive powders. Although the measurement of angle of repose has sometimes met industrial and academic needs for a simple and quick test that can disclose changes in the flow properties of powders as they pass through processing and handling equipment, Geldart et al (1990). Pointed out that there was no general agreement as to the best design or size of equipment, for the way that a test should be done, or the optimum amount of powder that should be used.

2.10.1 Basic Methods for AOR

The four most common methods in use until recently are shown in (Figure 2.4). In method, the powder is poured within the funnel which is caught at a constant height above the flat base while in method II the funnel is loaded with the test powder which is then increased gradually to allow the sample to flow out. Both these methods need that the powder must be capable to flow out of the small funnel and cohesive powder might not do so. Furthermore, the powders do not become aerated as they usually do in the production processes, but methods III and IV in which some ambient gas is entrained through the test. None of these methods is easy to calculate the angle in accurate way. Methods III and IV need equipment that should be mounted on a shaft passing through a low friction bearing so that it can be tilted gradually unto slipping happen and the angle calculated. The shaft and bearing usually necessarily to be dismantled for overall cleaning between tests, an inconvenience that slows down the testing procedure.

The most common methods for determining the static angle of repose can be classified on the basis of the following two important experimental variables:

1- The height of the “funnel” through which the powder passes might be fixed relative to the base, or the height may be different as the pile forms.
2- The base upon which the pile forms might be of fixed diameter or the diameter of the powder cone might be accepted to be different as the pile forms (GELDART et al., 1990).

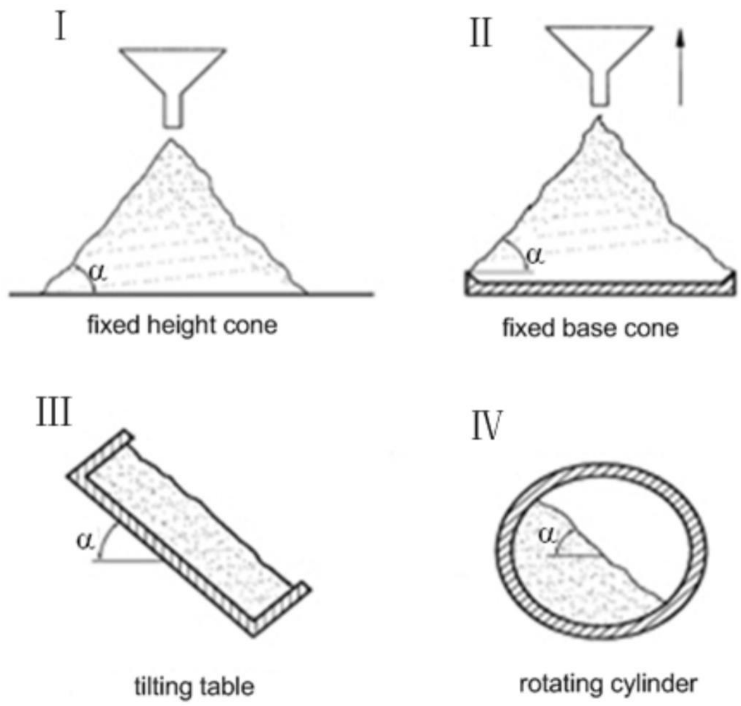


Figure 2.4: Measurement of static and dynamic angle of repose.

2.10.2 Variations in AOR Methods

Moreover, the above methods, the following differences have been used to many extents in the pharmaceutical literature:

- *Drained angle of repose* is specified via allowing an increase quantity of material positioned above a constant diameter base to "drain" from the container. Formation of a cone of powder on the fixed diameter base allows determination of the drained angle of repose.
- *Dynamic angle of repose* is specified via filling a cylinder (with a clear and flat cover on one end) and rolling it at a specified speed. The dynamic angle of repose is the angle (relative to the horizontal) created by the flowing powder.

The internal angle of kinetic friction is known by the plane isolating these particles sliding down the top layer of the powder and those particles that are rolling with the drum with roughened surface (Carr, R.L., 1965).

2.10.3 AOR General Scale of Flowability

There are many variations in the qualitative description of powder flow using the angle of repose, a lot of the pharmaceutical literature shows the consistent with the classification by (Carr, R.L., 1965), which is shown in (Table 2.1). There are examples in the literature of formulations with an angle of repose in the range of 40°- 50° that were manufactured satisfactorily. When the angle of repose exceeds 50°, the flow is rarely acceptable for manufacturing purposes.

Table 2.1: Flow Properties and corresponding angle of repose (after (Carr, R.L., 1965)).

Flow Property	**Angle of Repose (degrees)**
Excellent	25-30
Good	31-35
Fair—aid not needed	36-40
Passable—may hang up	41-45
Poor—must agitate, vibrate	46-55
Very poor	56-65
Very, very poor	>66

2.10.4 Recommended Procedure for AOR

Form the angle of repose on a fixed base with a retaining lip to retain a layer of powder on the base. The base should be without vibration. Change the height of the funnel to be carefully when built up a symmetrical cone of powder. Care must be to be free of vibration as the funnel is moved. The funnel height must be maintained approximately 2–4 cm from the top of the powder pile as it is being created in order to decrease the impact of falling powder on the tip of the cone. If a symmetrical cone of powder could not successfully or reproducibly prepared, then this method is not appropriate. Define the angle of repose by measuring the height of the cone of powder and calculating the angle of repose, α, from the following Equation (2.1):

$$\tan(\alpha) = \frac{\text{height}}{0.5\ \text{base}} \qquad (2.1)$$

2.10.5 Experimental Considerations for AOR

Angle of repose is not an intrinsic property of the powder; i.e., it is very much conditional onto the method that used to form the cone of powder. The following important considerations are raised in the existing literature:

- The peak of the cone of powder can be deformed by the impact of powder from above. By carefully building the powder cone, the deformation caused by impact will be decreased.

- The nature of the base onto which the powder cone is formed impacts the angle of repose. It is highly recommended that the powder cone be created on a “common base,” which can be accomplished by forming the cone of powder on a layer of powder. This will be done by using a base of fixed diameter with a protruding outer edge to hold a layer of powder onto which the cone is created (Geldart et al., 1990).

2.11 Compressibility Index and Hausner Ratio

In the last years the compressibility index and the Hausner ratio have become the easy, quick, and popular methods of foretelling powder flow characteristics. The compressibility index has been suggested as an indirect measure of bulk density, size and shape, surface area, moisture content, and cohesiveness of materials because all of these can influence the observed compressibility index. The compressibility index and the Hausner ratio are specified by measuring both the bulk volume and the tapped volume of a powder.

2.11.1 Bulk and Tapped Densities

We can measure bulk and tapped densities by three methods of each of them according to (USP. 616), and the most common:

Bulk Method 1: The bulk density is determined by adding a known mass of powder to a graduated cylinder. The density is calculated as mass/volume.

Tapped Method 1: The tapped density is determined by mechanically tapping a graduated cylinder containing the sample until little further volume change is noticed. We can perform the tapping by using different methods.

The tapped density is calculated as mass divided by the final volume of the powder. The interparticulate interactions that impact the bulking properties of a powder are also the interactions that interfere with powder flow. However, it is possible to gather information about the relative importance of those interactions in a given powder by comparing the bulk and tapped densities, and such a comparison it can be used to index the ability of the powder to flow (USP. 616, 2014).

2.11.2 Basic Methods for Compressibility Index and Hausner Ratio

Although there are some variations in the method of determining the compressibility index and Hausner ratio, the basic procedure is to measure:

a) Unsettled apparent volume (VO).

b) The final tapped volume (Vf), of the powder after tapping the material until no further.

The compressibility index and the Hausner ratio are calculated as follows in Equations (2.2) and (2.3) respectively:

Compressibility Index $=\frac{100\ (V0-Vf)}{V0}$ (2.2)

Hausner Ratio $=\frac{V0}{Vf}$ (2.3)

Alternatively, As seen in (Table 2.2) the Compressibility İndex and Hausner Ratio can be used to estimate the flow characteristics of the powder as well as measured using calculated values for bulk density (ρbulk) and tapped density (ρtapped) as follows in Equations (2.4) and (2.5) respectively:

Compressibility Index $=\frac{100\ (\rho\text{tapped} - \rho\text{bulk})}{\rho\text{tapped}}$ (2.4)

Hausner Ratio $=\frac{\rho\text{tapped}}{\rho\text{bulk}}$ (2.5)

Table 2.2: Scale of flowability (after (USP.35, 2012)).

Compressibility Index %	**Flow Character**	**Hausner Ratio**
1-10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.134
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very, very poor	>1.60

2.11.3 Recommended Procedure for Compressibility Index and Hausner Ratio

Using 250 mL in a volumetric cylinder with a test sample that weight of 100g. Smaller weights and volumes might be used, but differences in the methods must be described with the results. And taking an average of three determinations is recommended.

2.11.4 Experimental Considerations for the Compressibility Index and Hausner Ratio

Compressibility index and Hausner ratio are not intrinsic properties of the powder; i.e., they depend on the methodology that used. In the existing literature, there are discussions of the following important considerations affecting the determination of:

(1) The unsettled apparent volume (Vo).
(2) The final tapped volume (Vf).
(3) The bulk density (ρbulk).
(4) The tapped density (ρtapped):
   a) The diameter of the cylinder used.
   b) The number of times the powder is tapped to achieve the tapped density.
   c) The mass of material used in the test.
   d) Rotation of the sample during tapping. (USP.35, 2012).

2.12 Flow Through an Orifice

The flow rate of a material relies on to several factors, and there are two considerations which are particle related and process related. Controlling the rate of flow of any material through an orifice has been suggested as a better way to measure the powder flowability. The utility of controlling and monitoring continuously is very important because pulsating flow patterns have been recorded before even for free-flowing materials. Also, they observed some changes in flow rate as the container empties. Experimental equations relating flow rate to the diameter of the opening, particle size, and particle density have been determined. Yet, specifying the flow rate through an orifice is useful but only with free-flowing materials. The flow rate through an orifice is generally calculated as the mass per time flowing from any of a number of types of containers (cylinders, funnels, hoppers). Calculating the flow rate can be in separated increments or continuous.

2.12.1 Basic Methods for Flow Through an Orifice

The most common method for specifying the flow rate through an orifice can be classified on the basis of three important experimental differences:

(1) The type of container used to hold the powder such as cylinders, funnels, and hoppers from production equipment.

(2) The orifice diameter and shape, these are critical factors in specifying powder flow rate.

(3) The method of calculating flow rate, flow rate can be calculated continuously using an electronic balance with many sorts of recording devices (strip chart recorder, computer). It can also be calculated in separate samples (for example, the time it takes for 100 g of powder to pass through the orifice to the nearest tenth of a second or the amount of powder passing through the orifice in 10 seconds to the nearest tenth of a gram).

2.12.2 Variations in Methods for Flow Through an Orifice

We can determine either flow rate or volume flow rate. Mass flow rate is the easiest method, but it biases the results in favor of high-density materials. Because die fill is volumetric, specifying volume flow rate might be preferable. A vibrator is usually connected to facilitate flow from the container; yet, this shows to complicate interpretation of the results. To be more closely simulate rotary press conditions a moving orifice device has been suggested. The minimum diameter orifice through which powder flows can also be identified.

** There is no general scale for flow through an orifice because the flow rate is critically dependent on the method used to calculate it.

2.12.3 Recommended Procedure for Flow Through an Orifice

Flow rate through an orifice is not useful for cohesive material and it can be used only for materials that have some capacity to flow. AS long as the height of the powder bed (the “head” of the powder) is much greater than the diameter of the orifice, the flow rate is practically independent of the powder head. It is better to use a cylinder as the container because the cylinder material must have small effect on flow. These results in flow rate have been determined by the movement of powder over powder instead of powder over the wall of the container. When the height of the powder column is less than two times the diameter of the column powder flow rate usually increases. The orifice must be circular and the cylinder must be free of vibration. General guidelines for dimensions of the cylinder are as follows:

- Diameter of opening > 6 times the diameter of the particles.

- Diameter of the cylinder > 2 times the diameter of the opening.

In a production situation using a hopper as a container might be suitable and representative of flow. Using a funnel is not advisable, specially one with a stem, because flow rate will be specified by the length and size of the stem also the friction between the powder and the stem. A truncated cone might be suitable, but flow will be affected by the powder-wall friction coefficient, making selection of a suitable construction material an important consideration. And for the opening in the cylinder, use a flat-faced bottom plate with the choice to change orifice diameter to give maximum flexibility and to better ensure a powder-over-powder flow pattern. Rate measurement can be either separated or continuous. Continuous measurement using an electronic balance can be more effective to detect momentary flow rate variations (USP.35, 2012).

2.12.4 Experimental Considerations for Flow Through an Orifice

Flow rate through an orifice is not an essential property of the powder. Because it is very much depending on the methodology used. Many important considerations influencing these methods are discussed in the literature:

- The diameter and shape of the orifice.
- The type of container material (metal, glass, plastic).
- The diameter and height of the powder bed (USP.35, 2012).

2.13 Shear Cell Methods

In attempt to put powder flow studies and hopper design on much more fundamental basis, the differences of powder shear testers and methods that permit more exactly and precisely defined assessment of powder flow properties have been create a development. Shear cell methodology has been used a lot in the study of pharmaceutical materials. From these methods, several and wide set of parameters can be acquired, involving the yield loci representing the shear stress-shear strain relationship, the angle of internal friction, the unconfined yield strength, the tensile strength, and a set of derived parameters such as the flow factor and other flowability indices. Because of the ability to more precisely control experimental parameters, flow properties also can be specified as a function of consolidation load, time, and other environmental conditions. The methods have been successfully used to specify critical hopper and bin parameters.

2.13.1 Basic Methods for Shear Cell

One type of the shear cell is the cylindrical shear cell that is split horizontally, creating a shear plane between the lower stationary base and the moveable upper portion of the shear cell ring. And after powder bed consolidation in the shear cell (using a well-defined procedure), the force necessary to shear the powder bed by moving the upper ring is specified. Annular shear cell designs have some advantages more than cylindrical shear cell design, involving the need for less material. And the disadvantage is that because of its design, the powder bed is not sheared as uniformly and for example, material outside of the annulus is sheared more than material in the inside region. A third type of shear cell (plate-type) includes a thin sandwich of powder between a lower stationary surface and an upper moveable surface and they are rough surfaces. Each of the shear cell methods has advantages and disadvantages. As with the other methods for characterizing powder flow, several differences are described in the literature. A considerable advantage of shear cell methodology in general is a greater degree of experimental control. This methodology is:

1- Time consuming.

2- Demands considerable amounts of material.

3- Good trained operator.

2.13.2 Recommendations for Shear Cell

The several existing shear cell arrangements and test methods provide a lot of data and can be used very effectively to specify powder flow. They are also helpful in the design of equipment such as hoppers and bins. Because of the diversity of available equipment and experimental procedures, no specific recommendations regarding methodology are presented in this chapter. It is recommended that the results of powder flow characterization using shear cell methodology include a complete description of equipment and methodology used (USP.35, 2012).

CHAPTER THREE

EXPERTSYSTEMS

3.1 Introduction

'It is unworthy for men of excellence to labour like slaves over tasks that could be safely relegated to machines'. Liebnitz (1646–1716).

but

'If you turn to a computer to solve a problem you do not understand, all you're doing is transferring your lack of understanding to a technology you do not understand'Angell (1991).

Potential benefits of expert systems arise from the predicted advantages of artificial intelligence as follows:

- Permanence i.e. knowledge in an expert system is permanent, non-perishable and not affected by staff turnover. This benefit has been extrapolated to that of fewer skilled staff.
- Ease of duplication and dissemination i.e. knowledge in an expert system can be easily transferred across international borders in a form accessible to all. This benefit has been extrapolated to a reduced skill level.
- Consistency and reliability i.e. expert systems use all available, relevant information and do not overlook potential solutions. This benefit has been extrapolated to better quality of work.
- Ease of documentation i.e. decisions made in expert systems can be easily documented by tracing all the activities of the system. This benefit has been extrapolated to a training aid for novices (Roweet al., 1998).

- Rapid response i.e. computers can perform tasks at ever increasing speeds. This benefit has been extrapolated to increased output.
- Lower expense i.e. computer hardware is becoming less expensive. This benefit has been extrapolated to reduced costs as seen (Figure 3.1).

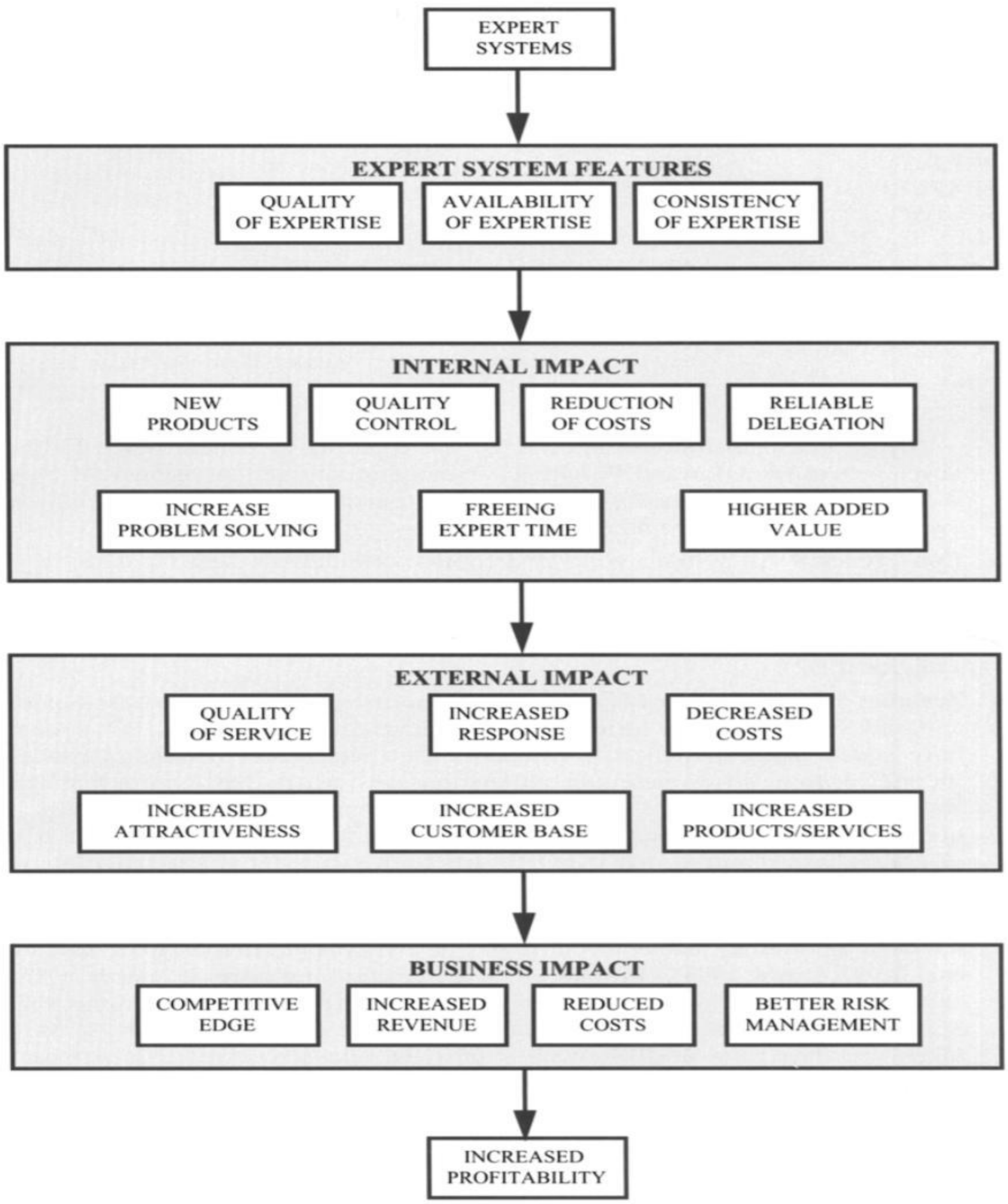


Figure 3.1: Impact of expert systems on business.

3.2 Expert System Definition

There is a wide variation of opinions as to defines an expert system. Most definitions can be divided into those that state what an expert system does and those that specify how it works; examples are:

‘An expert system is an intelligent computer program that uses knowledge and inference procedures to solve problems that are difficult enough to require significant human expertise for their solutions’ (Feigenbaum, 1982).

‘An expert system is a knowledge-based system that emulates expert thought to solve significant problems in a particular domain of expertise’ (Sell, 1985).

‘An expert system is a computer program that assists the user by providing information about a particular domain. It does this by manipulating information about the field that has been provided by a number of experts in the field. Another important feature of an expert system is that it has the facility to explain/justify the methods it used to provide the information’ (Doukidis and Whitley, 1988).

‘An expert system is a computer program that represents and reasons with knowledge of some specialist subject with a view to solving problems or giving advice’ (Jackson, 1990).

‘An expert system is a computer program that draws upon the knowledge of human experts captured in a knowledge-base to solve problems that normally require human expertise’ (Partridge and Hussain, 1994).

‘An expert system is a computer system that applies reasoning methodologies or knowledge in a specific domain in order to render advice or recommendations, much like a human expert’ (Turban, 1995).

‘A computer program capable of making recommendations or decisions based on knowledge gathered from experts in the field’ (Çelik, 1996).

Because of their emphasis on knowledge, expert systems are also known as knowledge-based or knowledge-based information systems and many authors use the terms interchangeably.

3.3 Expert System Features

In systems where knowledge is generally obtained through non-human intervention e.g. by information systems, the term knowledge-based system is more suitable. Following on from these definitions is a group of features which Jackson (1990) states are ‘sufficiently important that an expert system should really exhibit all of them to some degree:

- It should be simulating human reasoning about a problem domain, rather than simulating the domain itself.
- It should be proceeding reasoning over representations of human knowledge, in addition to doing numerical calculations or data recovery.
- It should be solving problems by heuristic or approximate methods which, unlike algorithmic solutions, are not guaranteed to succeed.
- It should be deals with subject matter of a true complexity that normally demand a considerable amount of human expertise.
- It should be show high performance in terms of speed and reliability in order to be a useful tool.
- It should be qualified for explaining and justifying solutions or recommendations to convince the user that its reasoning is correct (Jackson, 1990).

3.4 Expert System Domains

Expert systems can domain and address several problems includes:

1. **Prediction:** The inference of likely consequences of given situations e.g. weather forecasting.
2. **Diagnosis:** The inference of a system malfunction from observations e.g. medical diagnosis.
3. **Design:** The configuration of objects that satisfy defined constraints for example, product formulation.
4. **Interpretation:** The inference of situation descriptions from observations for example, image analysis.
5. **Planning:** The development of actions to achieve goals for example, product management.
6. **Repair/correction:** The definition of appropriate remedies for a diagnosed problem for example, solution to problems.
7. **Monitoring:** The comparison of observations to defined targets for example, air-traffic management.
8. **Control:** The management of the overall behavior of a system including monitoring and interpreting the current situation, predicting the future, diagnosing the causes of problems and correcting faults for example, control of any manufacturing process (Turban, 1995).

3.5 Expert System Components

In their simplest form the expert systems, have three components: an interface, an inference engine and a knowledge base. These components and the three human elements relationship involved in the development and use of expert systems is shown diagrammatically in (Figure 3.2). For an expert system to be of any use it should be capable to communicate with both the user and the developer (knowledge engineer). This is maybe done directly by a screen and keyboard or indirectly by external links to equipment/machines/monitoring device.

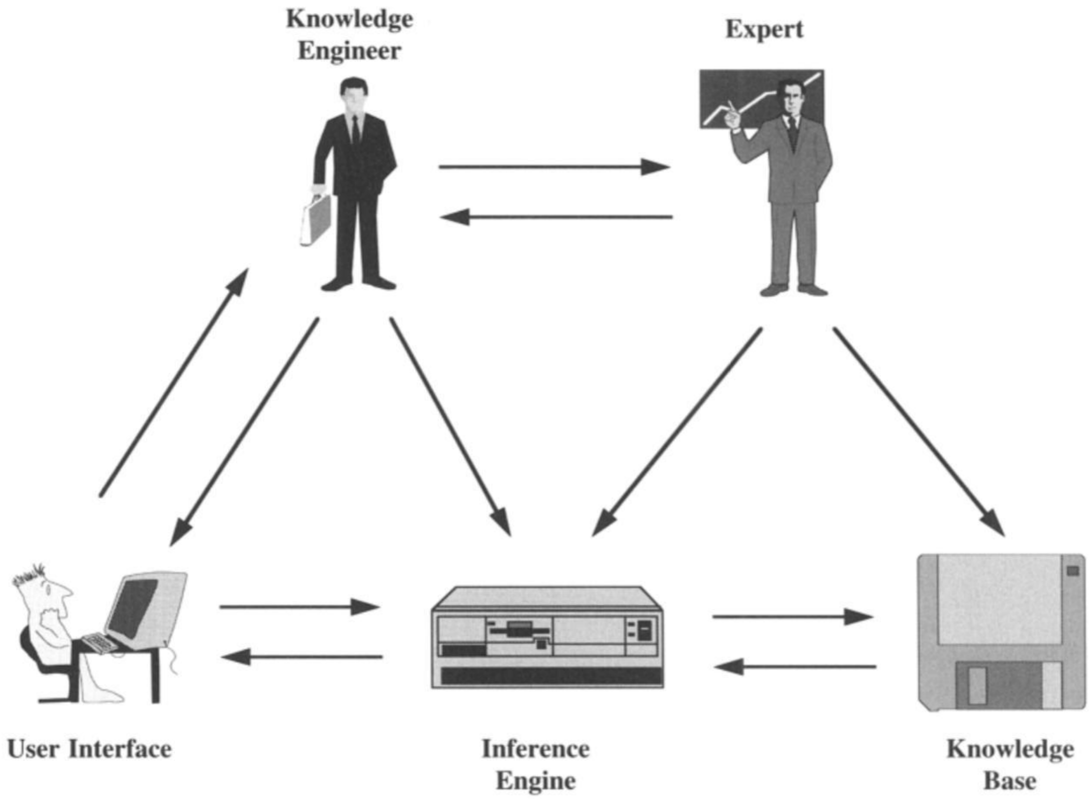


Figure 3.2: The relationship between the components of an expert system and the three human elements involved in its development.

The type of interface will be based on the nature and degree of interaction; the user will generally demand an interface that will be easy and friendly to use authorizing two ways of communication as in a question and answer routine, and the knowledge engineer will generally demand an interface that is efficient and operational. In the inference engine, the knowledge that gathered from the knowledge base is extracted and manipulated and new information produced i.e. the inference engine simulates the process to solve the problem in hand. There are two main oncoming for controlling inferencing in rule-based expert systems: forward chaining and backward chaining. The first, usually described as data-driven reasoning, is used for problem solving when data or basic ideas gained from consultation with the user are the starting point. The system then efforts to arrive at conclusions or goals. A problem with forward chaining is that every goal possible is highlighted whether useful or not. In the other hand, backward chaining, usually described as goal-directed reasoning, starts with a hypothesis or specific goal and then efforts to find data from consultation with the user to prove or disprove the conclusion. While forward chaining is usually used in expert systems for design (for example, product formulation) backward chaining is specifically useful to diagnostic, control or monitoring systems. Yet, in most developed systems both inferencing methods are used maybe singly or combined see (Table 3.1). Also, most inferencing engines have the ability to reason in the existence of uncertainty both in the input data and also in the knowledge base. The major methods used are Bayesian probabilities and fuzzy logic.

Table 3.1: Backward vs Forward chaining (after (Jackson, 1990)).

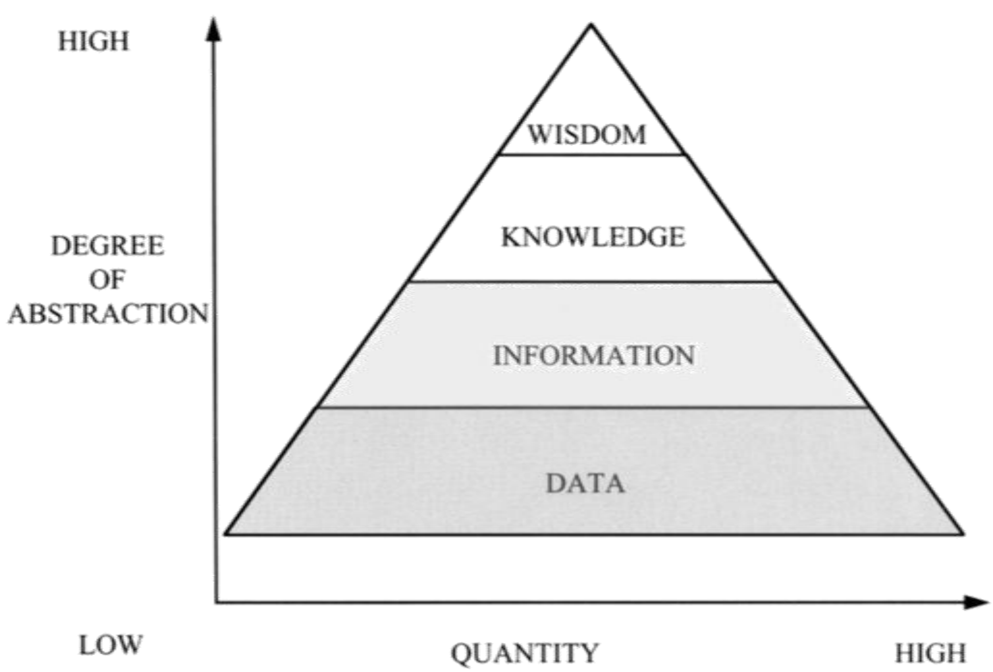
Attribute	Backward Chaining	Forward chaining
Also known as	Goal-driven	Data-driven
Starts from	Possible conclusion	Somewhat wasteful
Aims for	Necessary data	(Any conclusions)
Approach	Conservative/cautious	Opportunistic
Practical if	Number of possible final answers is reasonable or a set of known alternatives is available	Combinatorial explosion creates an infinite number of possible right answers
Appropriates for	Diagnostic, prescription and debugging application	Planning, monitoring, control and interpretation application
Examples of application	Selecting a specific type of investment	Making changes to corporate

3.6 Knowledge Engineering

Knowledge in any science always takes the form of facts, rules and heuristics; the facts includes the objects and the concepts about which the expert reasons, the rules and heuristics (usually referred to as rules of thumb) are derived from this reasoning. The difference between rules and heuristics is based on the validity and rigor of the arguments used to justify them— rules are always true, valid and can be justified by rigid argument; heuristics are the expert's best judgement, and might not be valid in all cases and can only be justified by examples. Associated with these are the terms data and information. While data refers to facts and figures, information is data transformed by processing and organized so that it is important to the person receiving it.

Knowledge can subsequently be considered as information combined with heuristics and rules. Also, more abstract is wisdom which can be considered as knowledge tempered by judgement and supplemented by experience and learning (Partridge and Hussain, 1994). These concepts can be classified by their degree of abstraction and by their quantity as seen in (Figure 3.3).

Figure 3.3: The classification of data, information, knowledge and wisdom.



There are two levels of knowledge: **shallow or surface knowledge** as its name proposes, is an exemplification of only surface-level information and it can be only transactingwith very specified situations, and **deep knowledge** is an exemplification of all the information connecting to a domain. It can include such human characteristics as emotion and intuition and hence is difficult to structure in a computer.

And there are three main groups: declarative, procedural and metaknowledge:

1. **Declarative knowledge** is a descriptive exemplification of the facts connecting to a domain and is considered shallow in nature.
2. **Procedural knowledge** is a detailed group of instructions on how to carry out a procedure.
3. **Metaknowledge is knowledge** about knowledge: knowledge about how a system operates or reasons. It is especially useful in generating explanations.

All of this knowledge about a specific domain is in the form of expertise (usually collected over many years of work) resident with the domain expert or, in the case of large complex domains, a number of experts. It is the objective of the knowledge engineer to set or elicit this knowledge from the experts and other sources and structure it in the computer such that it can be used by non-experts (Partridge and Hussain, 1994)

3.7 Knowledge Acquisition

The first step in knowledge acquisition is to gather all the possible sources of knowledge as describe in (Figure 3.4). Those including all written documents i.e. books written specifically in the domain, research and technical reports, reference manuals, case studies and even standard operating procedures and organizational policy statements. Availability of written documents differ from case to case; in some domains there might be several available, and in others none at all. Written documents contain actual knowledge; they are usually particular, accurate and well-structured but are not always relevant for the knowledge acquisition task. Whatever, if considerable written documents exist, their utilization is time and cost effective particularly in allowing the knowledge engineer to gain a wide view of the domain. Knowledge can also be obtained from discussion with organizational personnel e.g. the project sponsor, the project leader and various consultants. Otherwise, the most important source of knowledge is the domain expert or experts. In general, two types of knowledge might be gathered from these people.

1. **Explicit knowledge:** knowledge that the domain expert is aware of having and is able to articulate.
2. **Tacit knowledge:** knowledge that the domain expert is not aware of having but does exist as proved by the expert's known ability of solving problems in the application domain.

Explicit knowledge is very easy to gather from the experts since it is mainly actual in nature. Tacit knowledge is hard to identify and gather but it is major for the successful development of expert systems. In gathering both types of knowledge the knowledge engineer should be conscious that all verbal data gained is usually imperfect i.e. knowledge can be:

- Incomplete since experts usually forget.
- Superficial since experts usually cannot articulate in detail.
- Imprecise since experts might not know the accurate detail.
- Inconsistent since the experts usually fall into contradictions.
- Incorrect since experts might be wrong.
- usually unstructured since experts usually cannot indicate their knowledge in a systematic fashion, usually jumping from one topic to another.

The decision to employ one or more experts in the knowledge acquisition process is a difficult decision since there can be both advantages and disadvantages with this approach. Multiple experts obviously have the advantage of giving a greater dividing of work, different opinions/ expertise, minimizing individual bias but display a completeness to the knowledge base. However, this can be driving to raise the costs and disruption to the function. There are usually logistical problems in having everybody together at the same time. In addition, different opinions/expertise and personal incompatibilities can usually driving to incompatible viewpoints, hard to reconcile. For small domains it is usually enough to use one expert to evolve the system, but to use others in the evaluation stage. However, for large complex domains multiple experts should be considered (Turban, 1995).

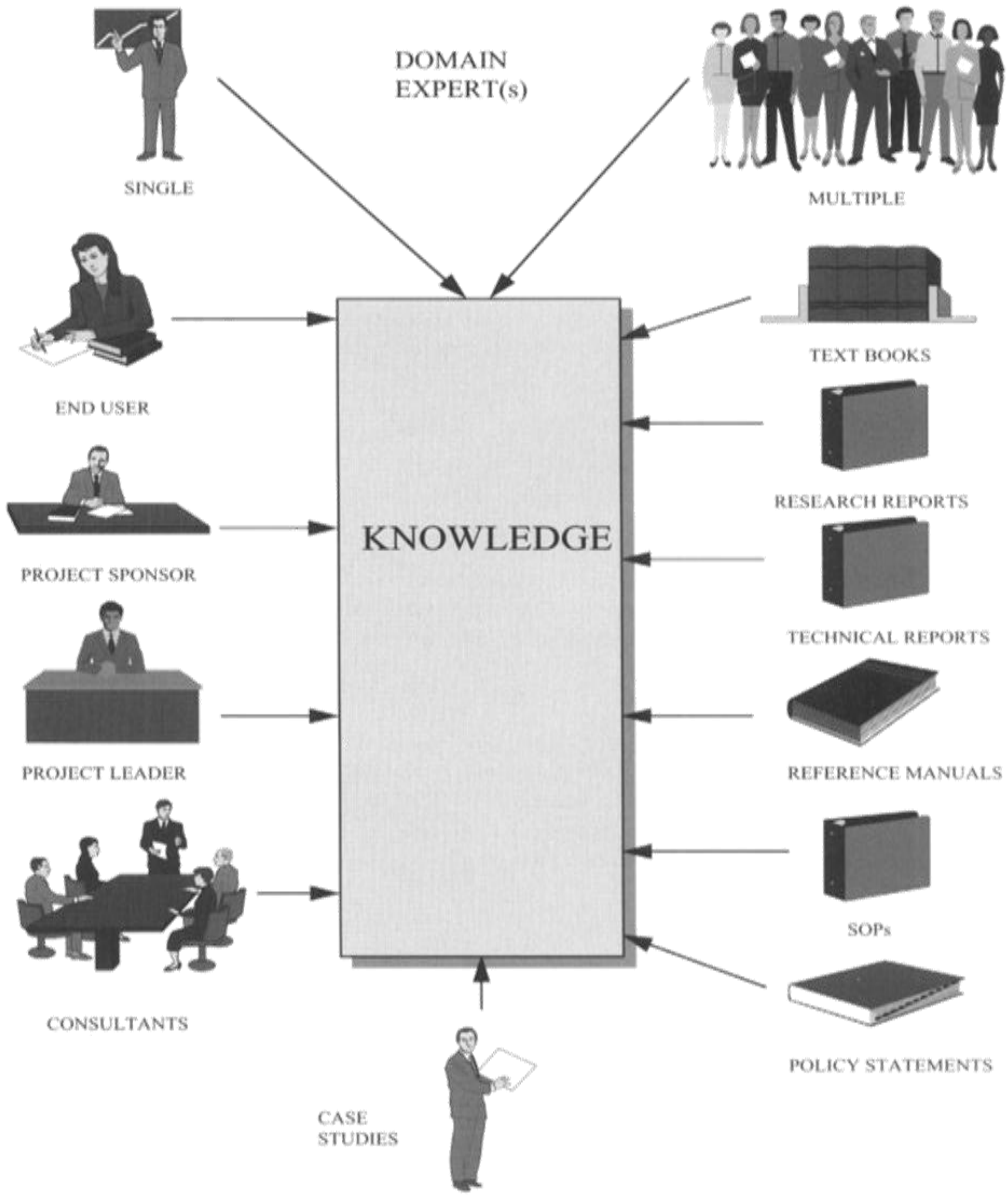


Figure 3.4: Source of knowledge.

There are particular characteristics necessary for the domain expert or experts. If the knowledge acquisition process is to be successful the experts should:

- Having a deep knowledge of the domain.
- Be ready to engage in the development of the expert system.
- Be convinced of the importance of the project.
- Having strong interpersonal skills.
- Be allowed time to engage in the project and be supported in this by management at all levels.

This is essential since the development of an expert system is time consuming. Coupled with these are the needed skills of the knowledge engineer:

- A deep knowledge of the technology engaged in the development of expert systems.
- Good communication skills.
- Fast learning and logical thinking.
- Sensitivity and diplomacy.
- Patience and tolerance.
- Organized and persistent.
- Good interviewing skills (O'Neill 1989).

3.8 Decision Tree

In a decision tree knowledge is organized in a spreadsheet format using columns and rows, the columns representing the attributes and the rows representing the conclusion. Once constructed the knowledge in the table can be used as input to other knowledge representation methods. It may also be used for rule induction. Decision trees are related to decision tables and can be constructed from them using rule induction algorithms. A decision tree is composed of nodes representing the goals and links representing decisions i.e. at each node there is an explicit question to answer and the actual answer given determines which of the alternative subsequent nodes is selected at the next decision point. Decision tables and trees are easy to understand and program. The techniques do not work well for complex systems because they become unwieldy and difficult to interpret Sell, 1985).

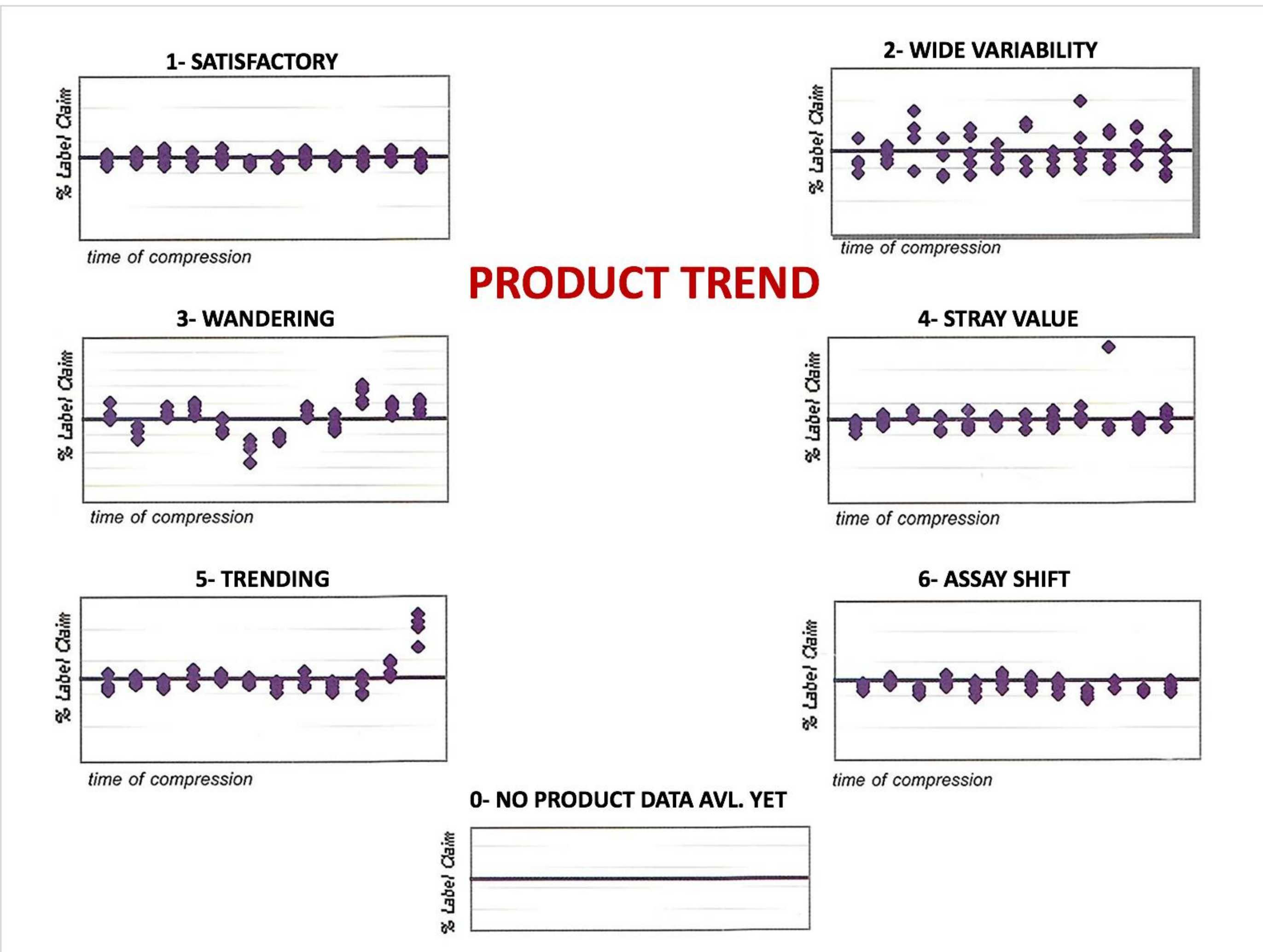
CHAPTER FOUR

MATERIALS AND METHODS

4.1 Material and Methods

There is no material, but using a certain method to identify common product uniformity and blend uniformity profiles for flow see (Figure 4.1 and 4.2).

Figure 4.1: Product trend profiles.



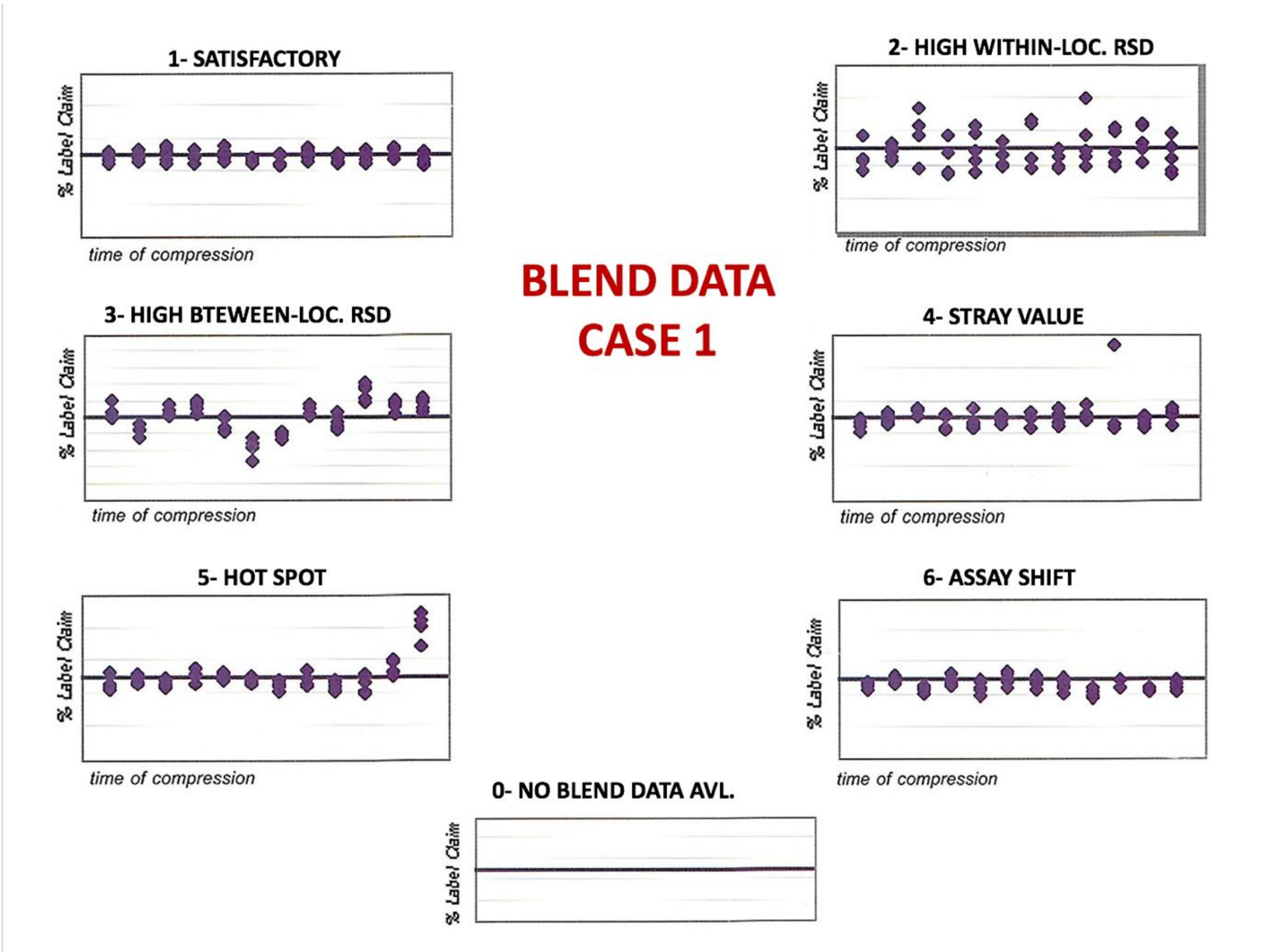


Figure 4.2: Blend data profiles.

According to these profiles should come up with 48 cases and in the expert system also can call it 48 decision trees:

Figure 4.3: Decision tree REF. 1.1

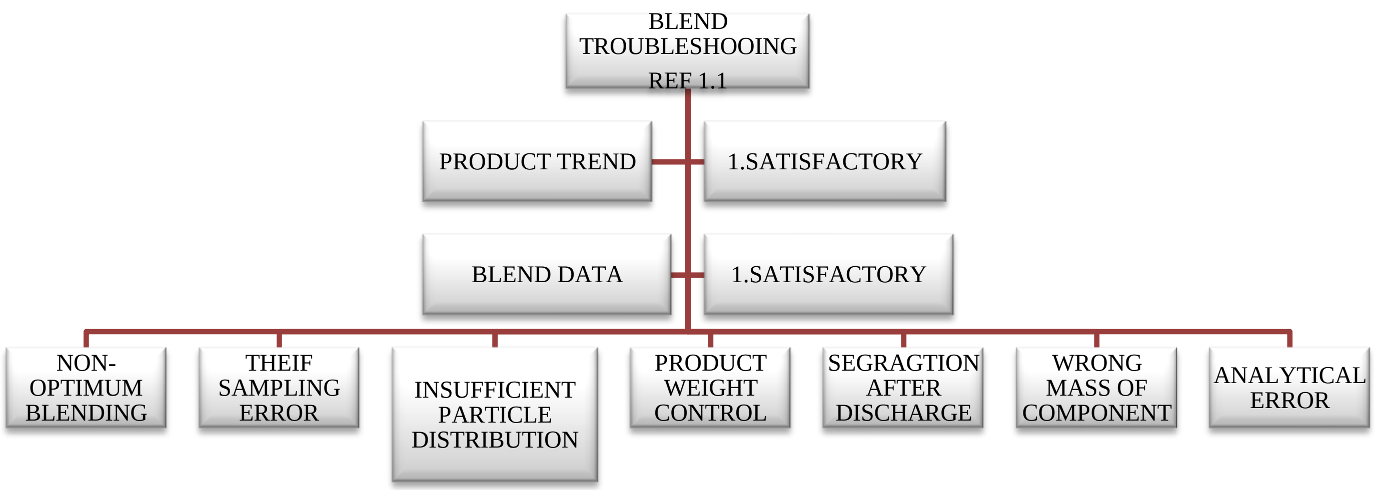


Figure 4.4: Decision tree REF. 1.2

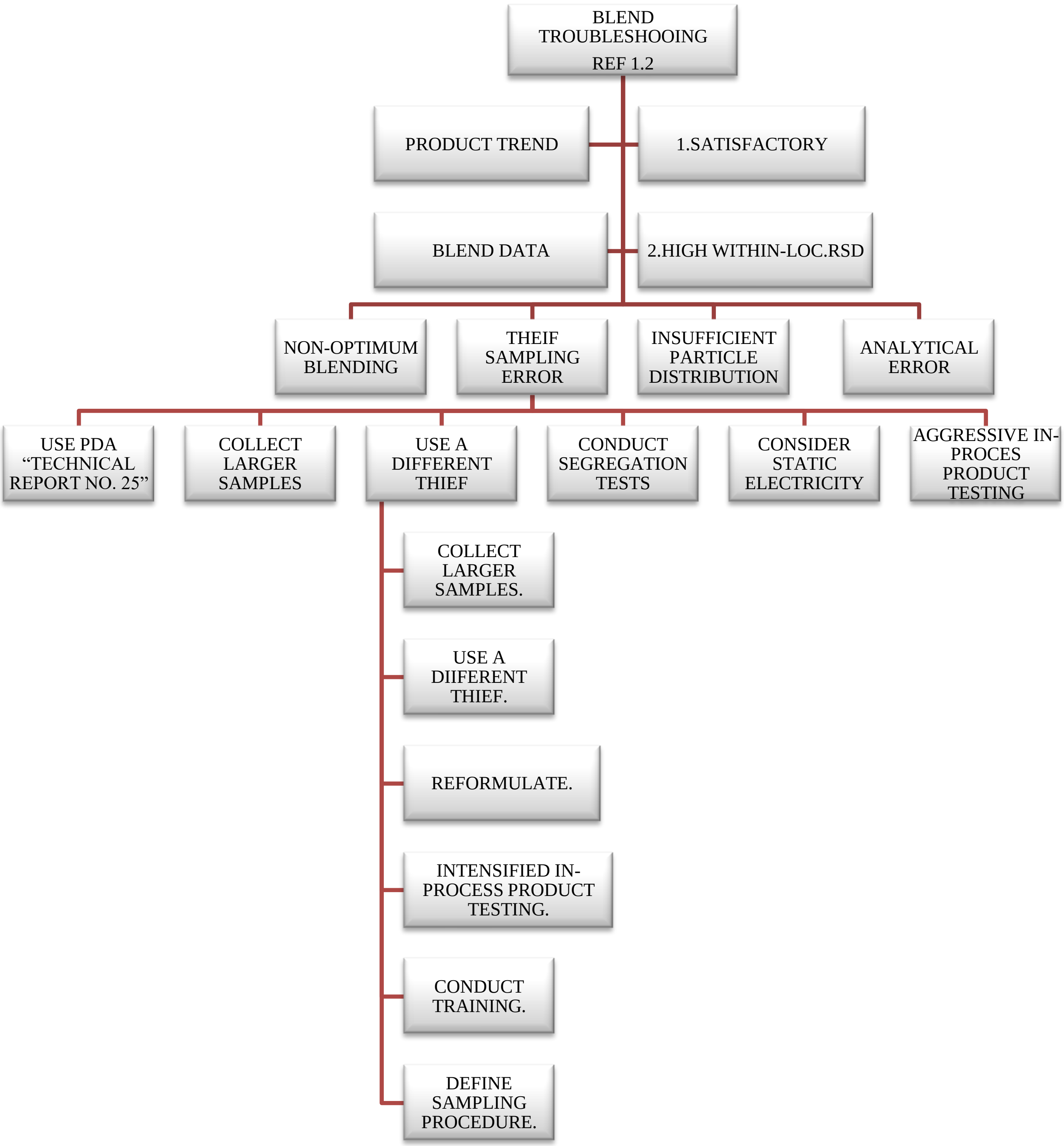


Figure 4.5: Decision tree REF. 1.3

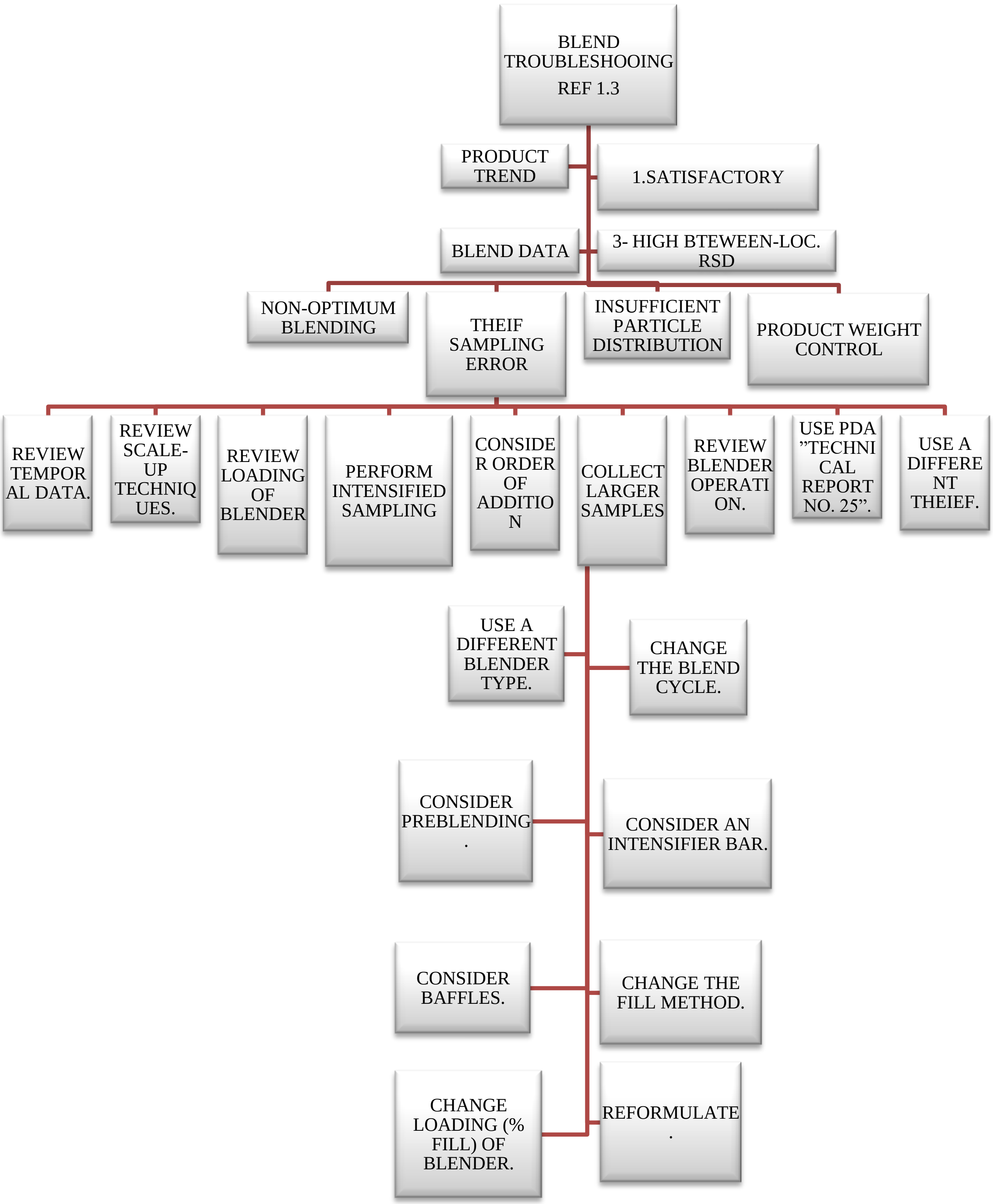


Figure 4.6: Decision tree REF. 1.4

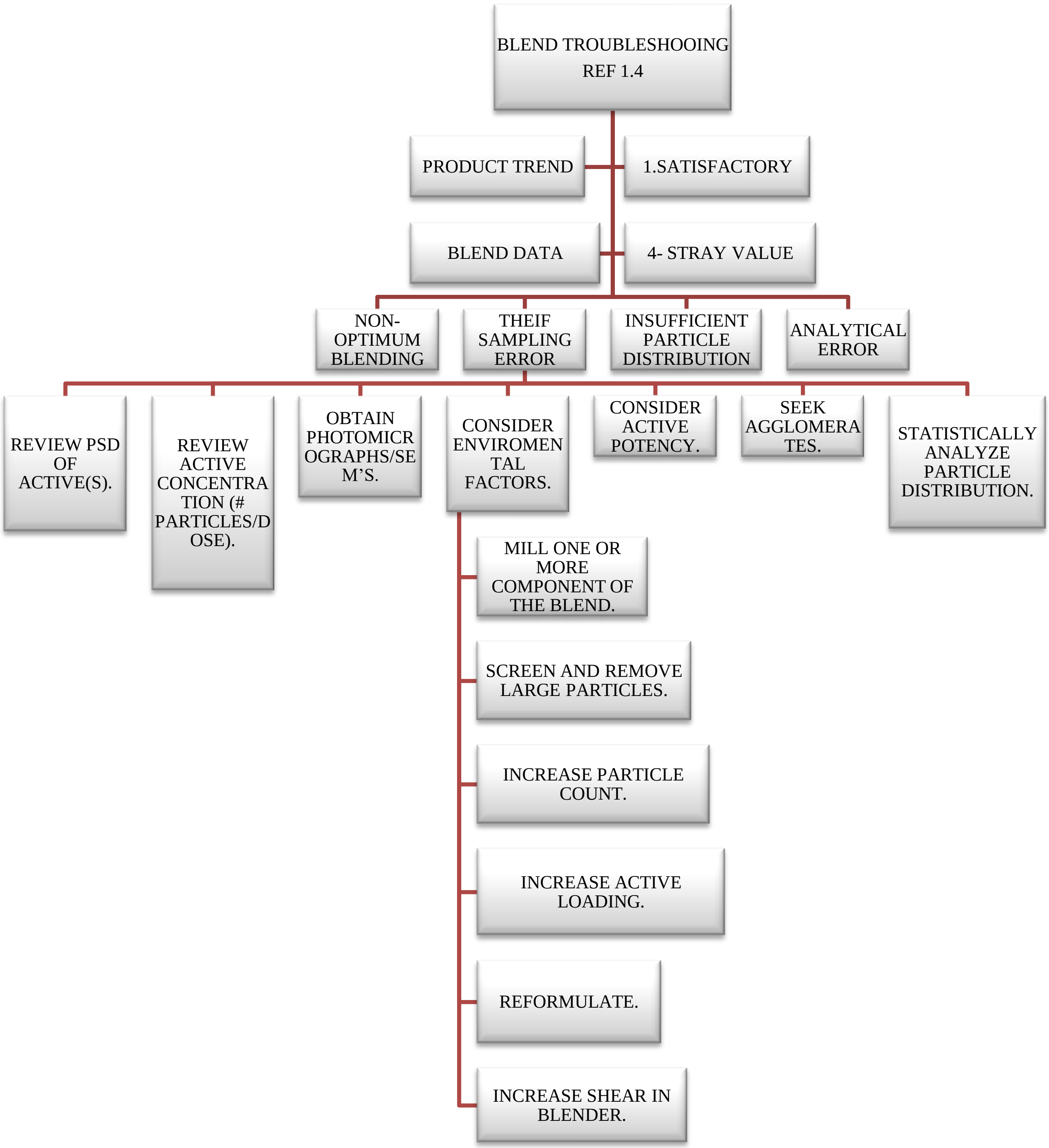


Figure 4.7: Decision tree REF. 1.5

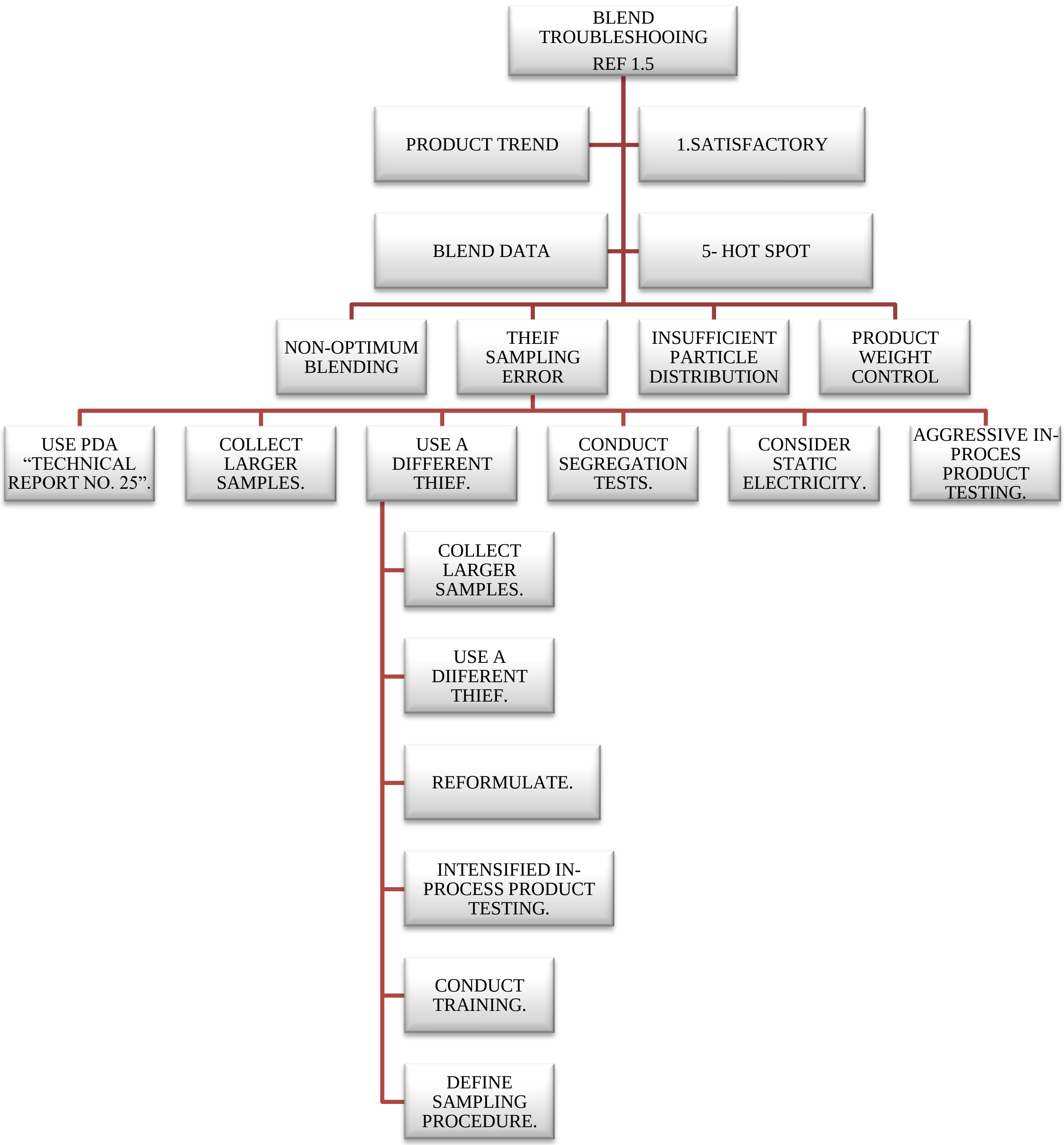


Figure 4.8: Decision tree REF. 1.6

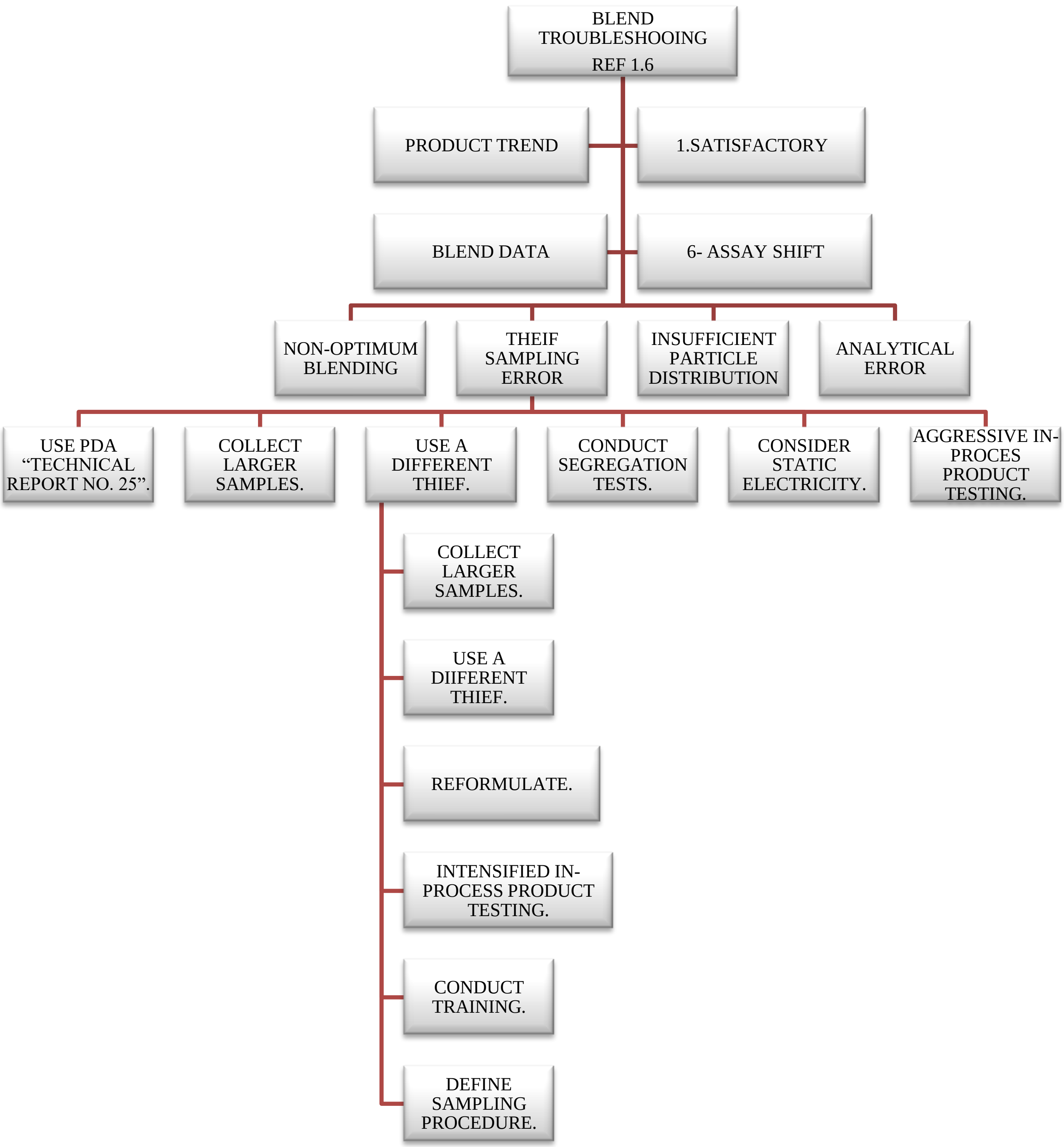


Figure 4.9: Decision tree REF. 1.0

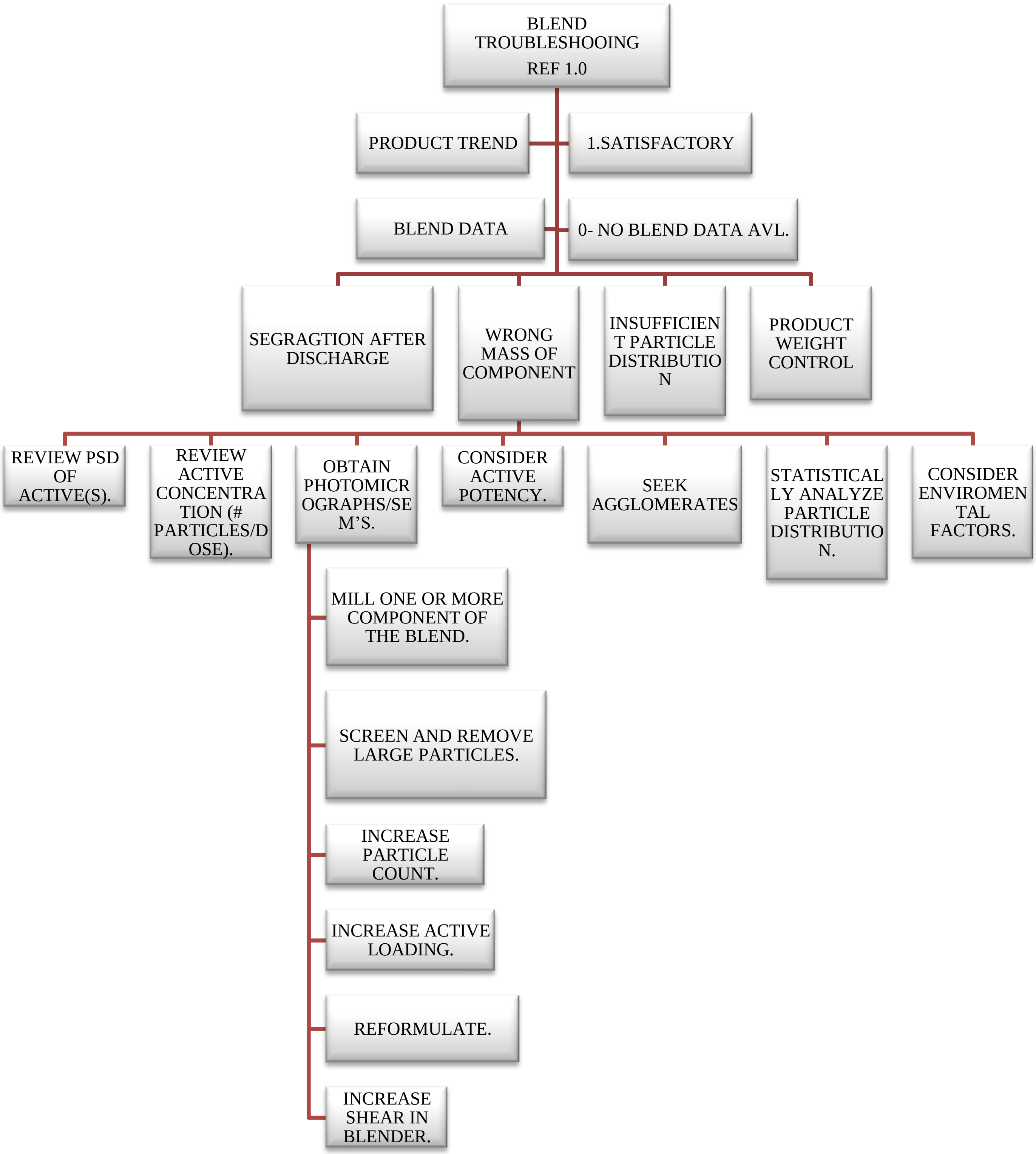


Figure 4.10: Decision tree REF. 2.1

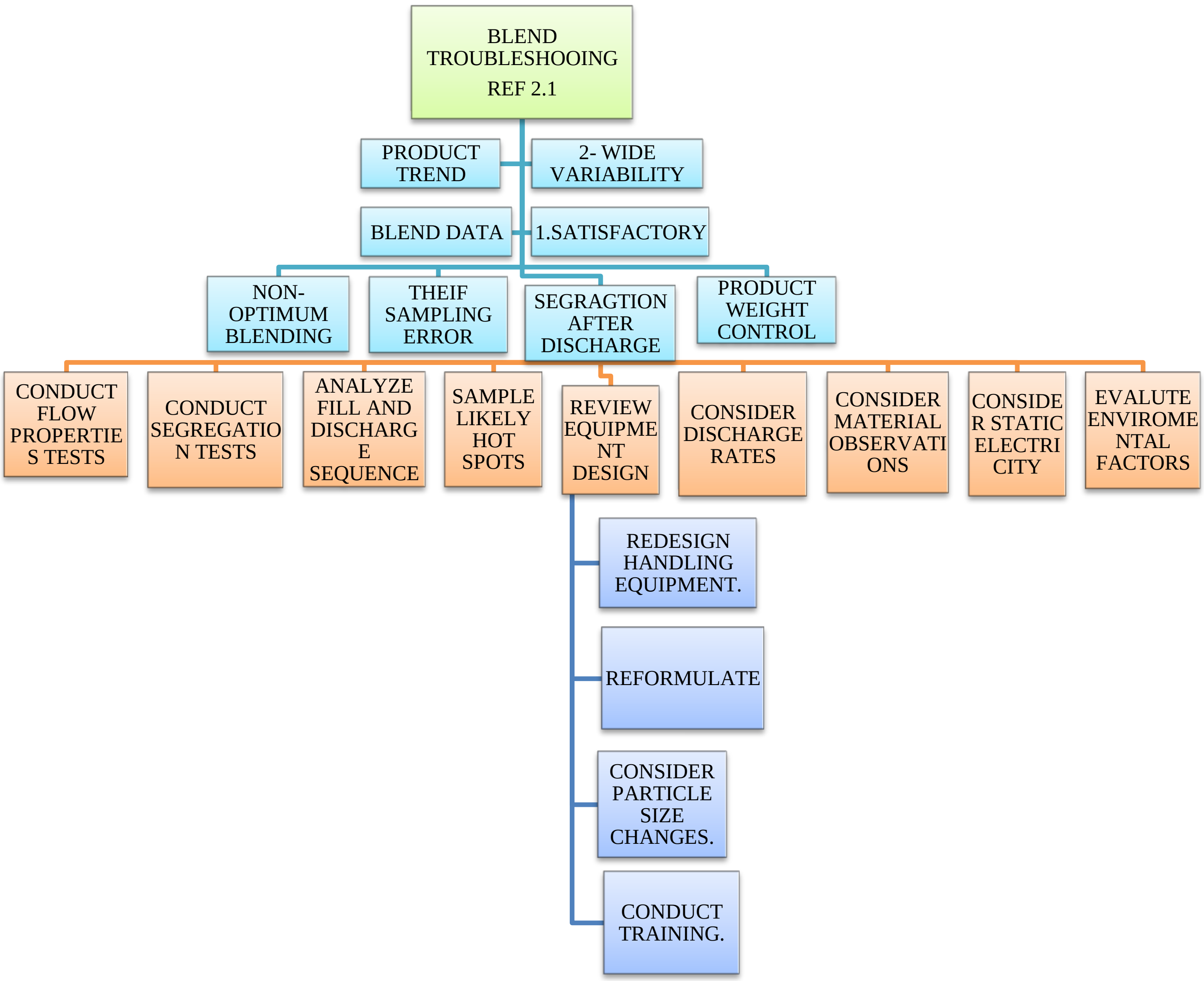


Figure 4.11: Decision tree REF. 2.2

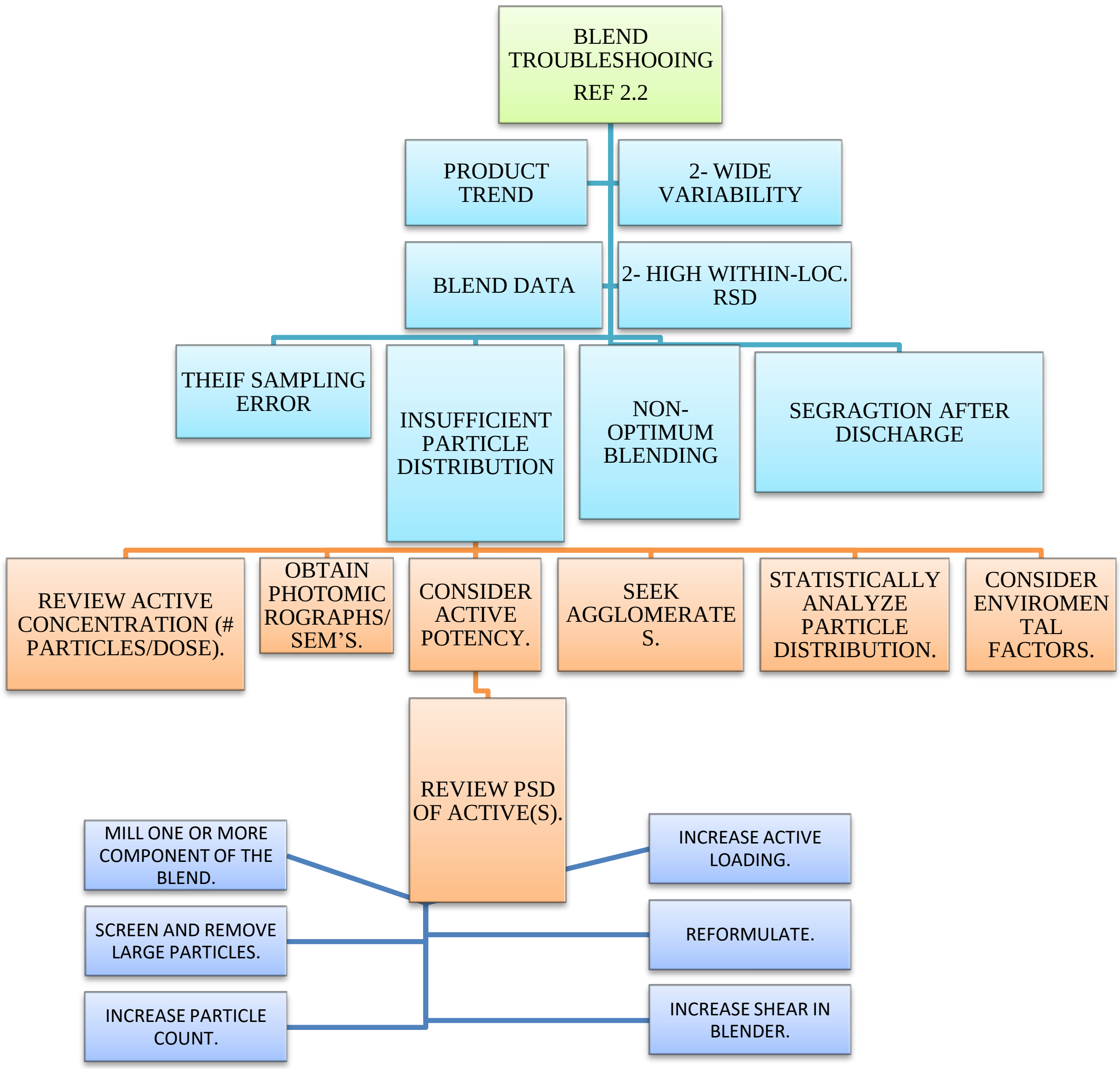


Figure 4.12: Decision tree REF. 2.3

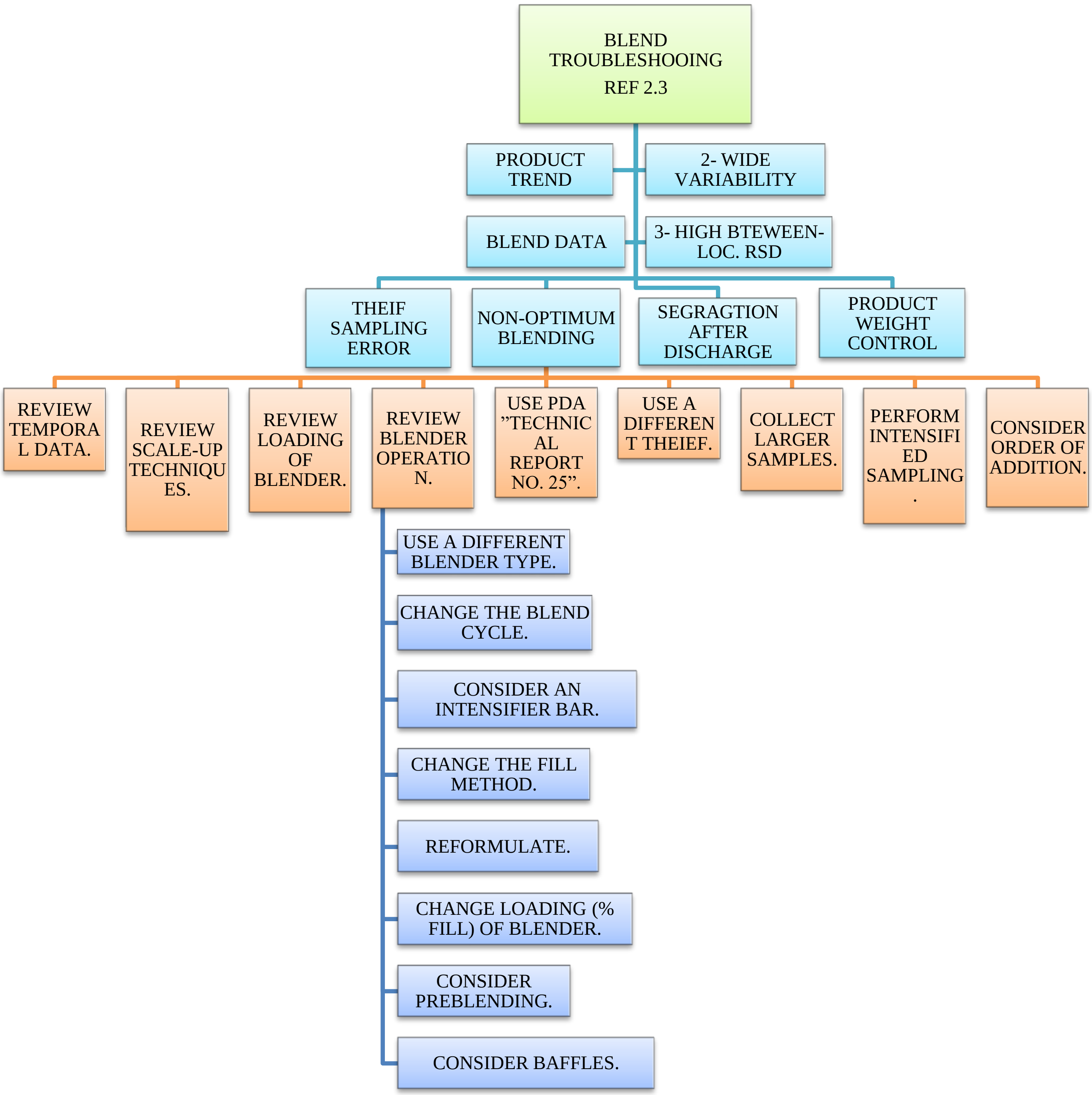


Figure 4.13: Decision tree REF. 2.4

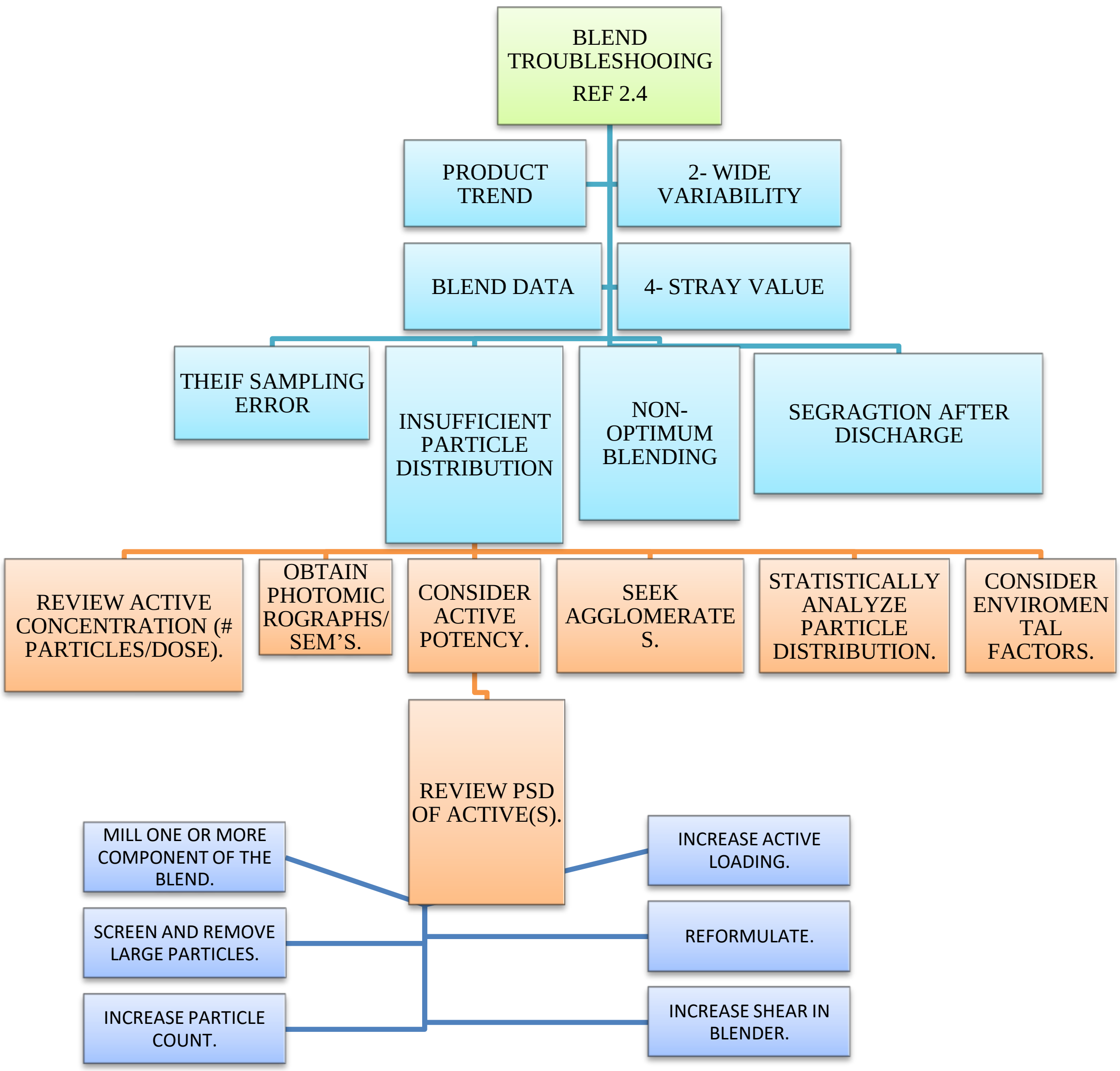


Figure 4.14: Decision tree REF. 2.5

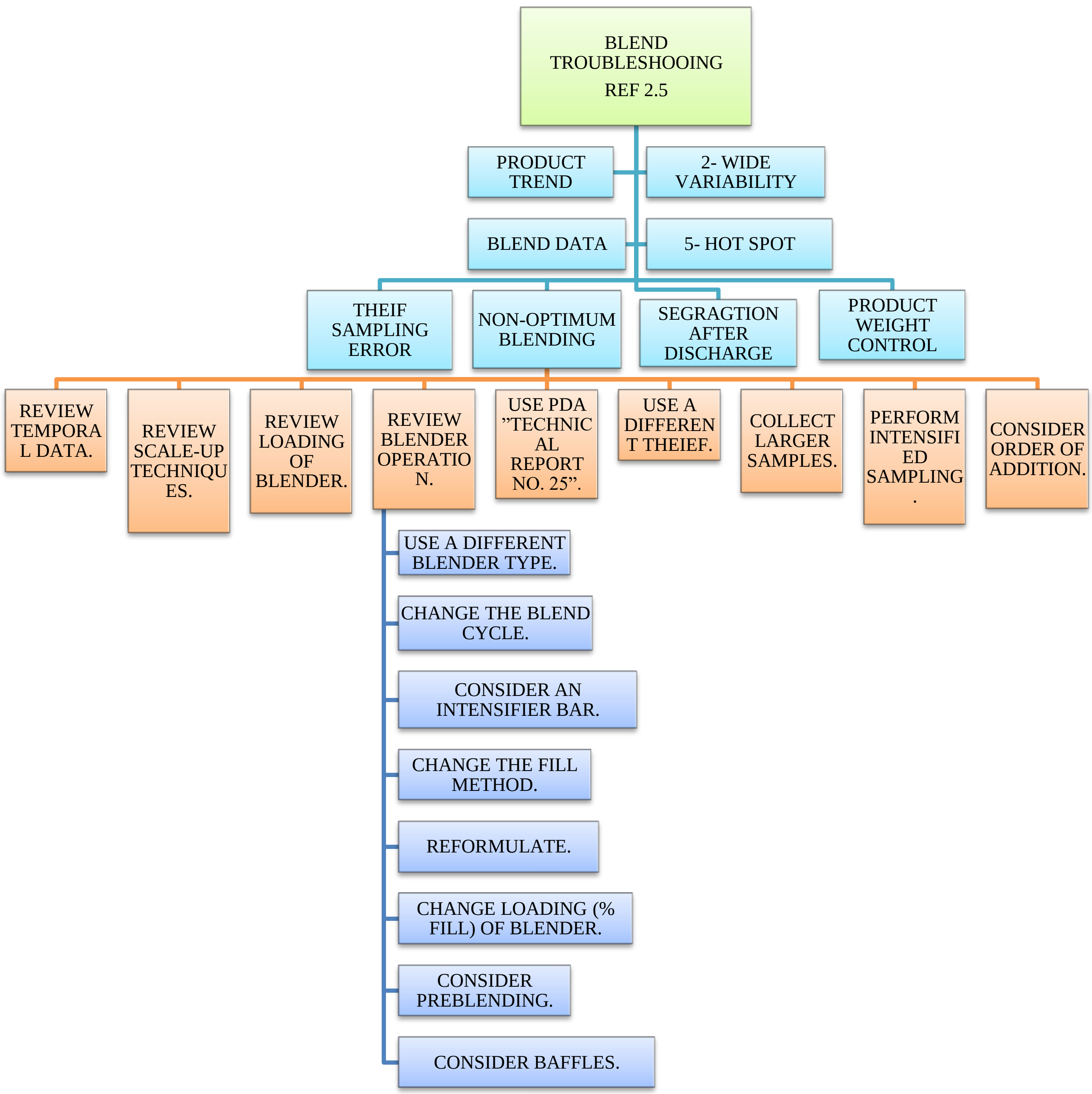


Figure 4.15: Decision tree REF. 2.6

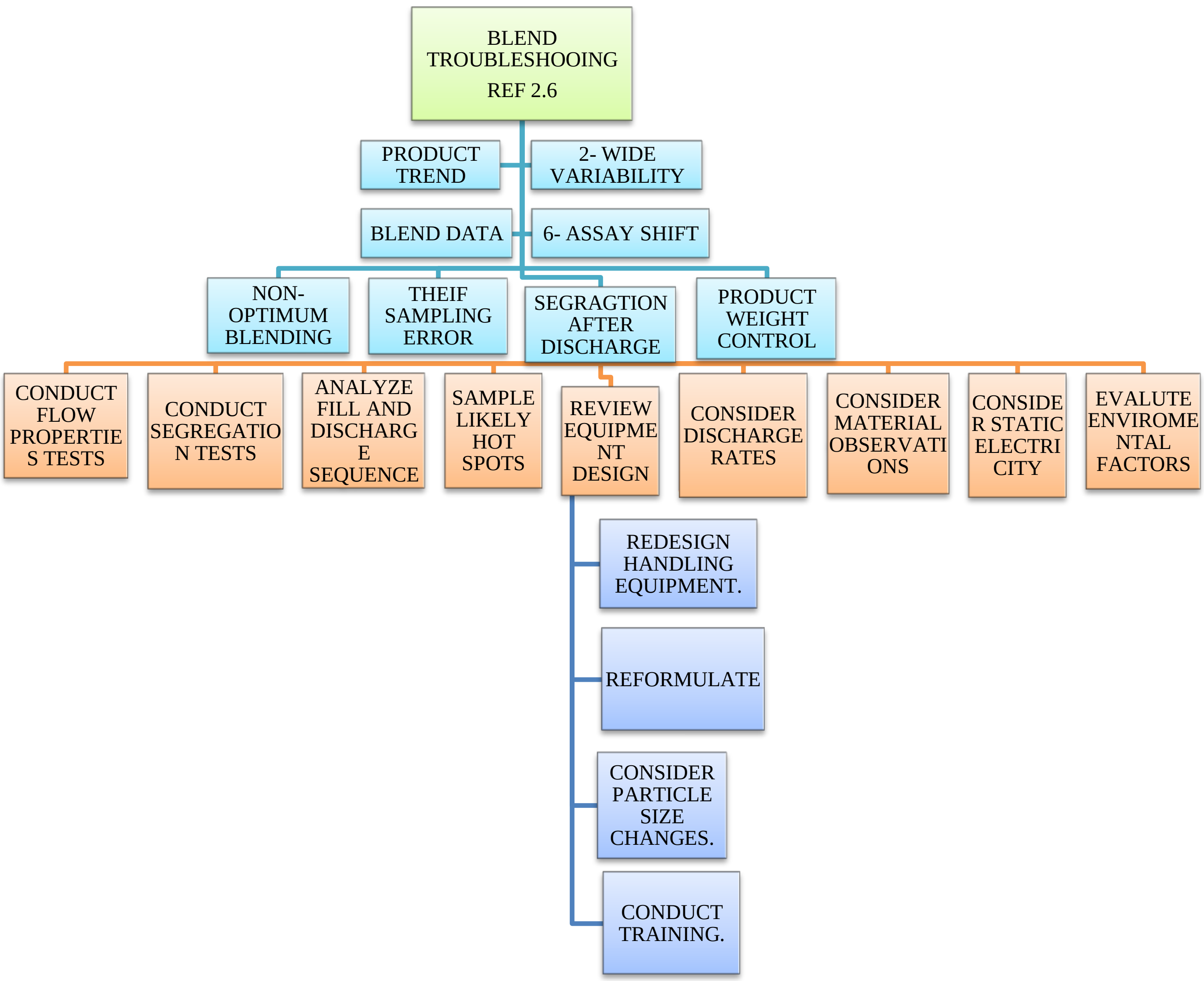


Figure 4.16: Decision tree REF. 2.0

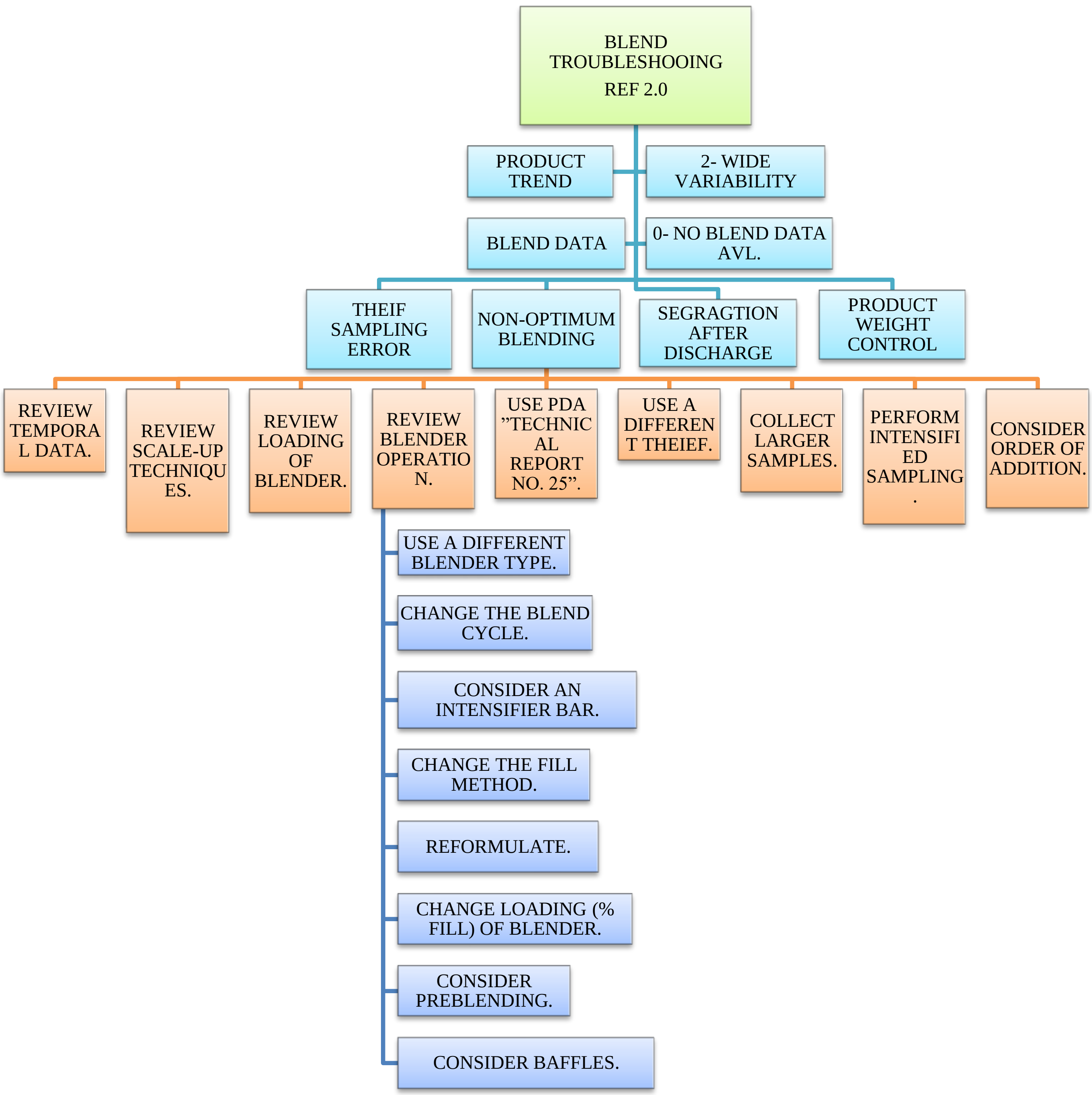


Figure 4.17: Decision tree REF. 3.1

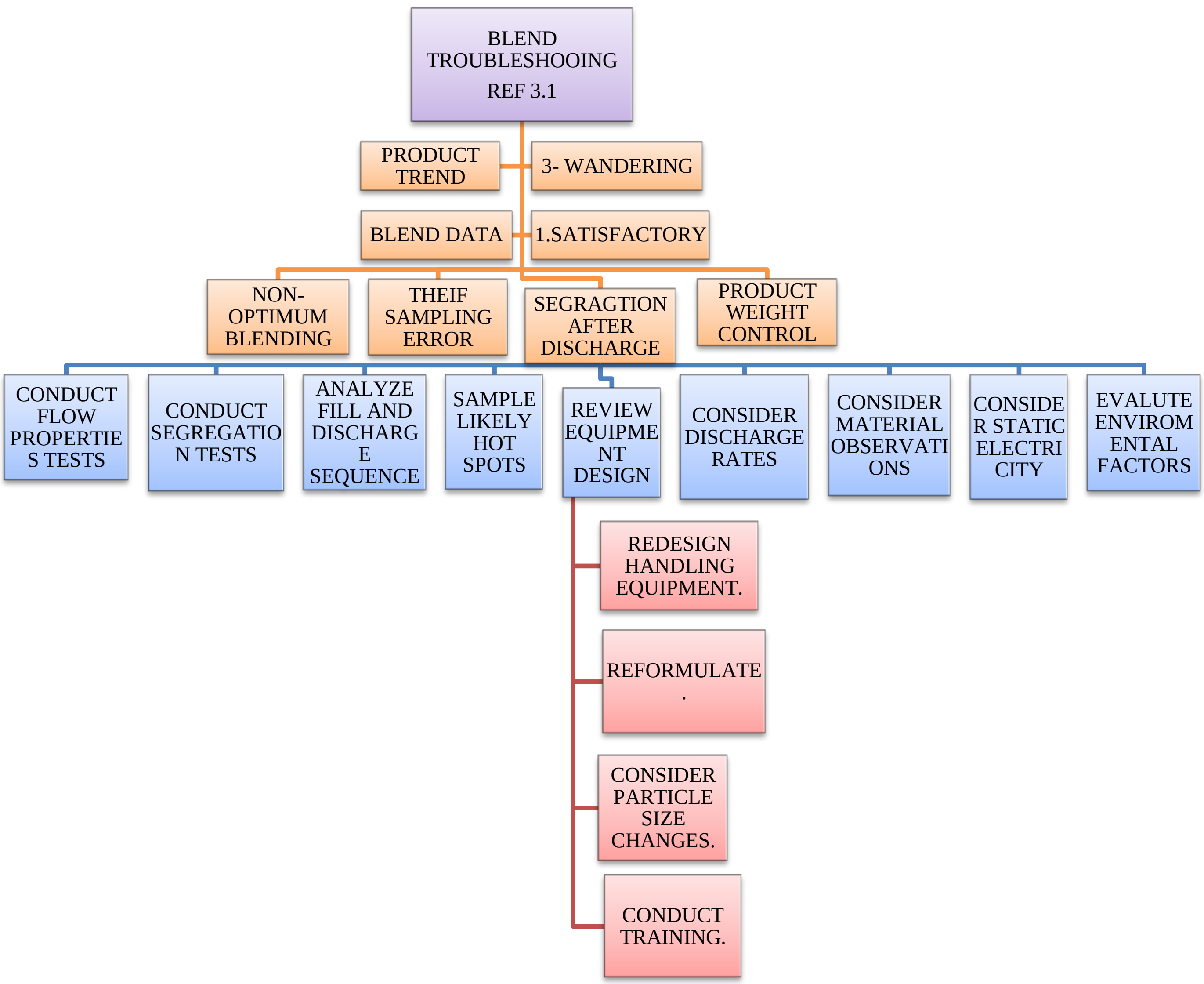


Figure 4.18: Decision tree REF. 3.2

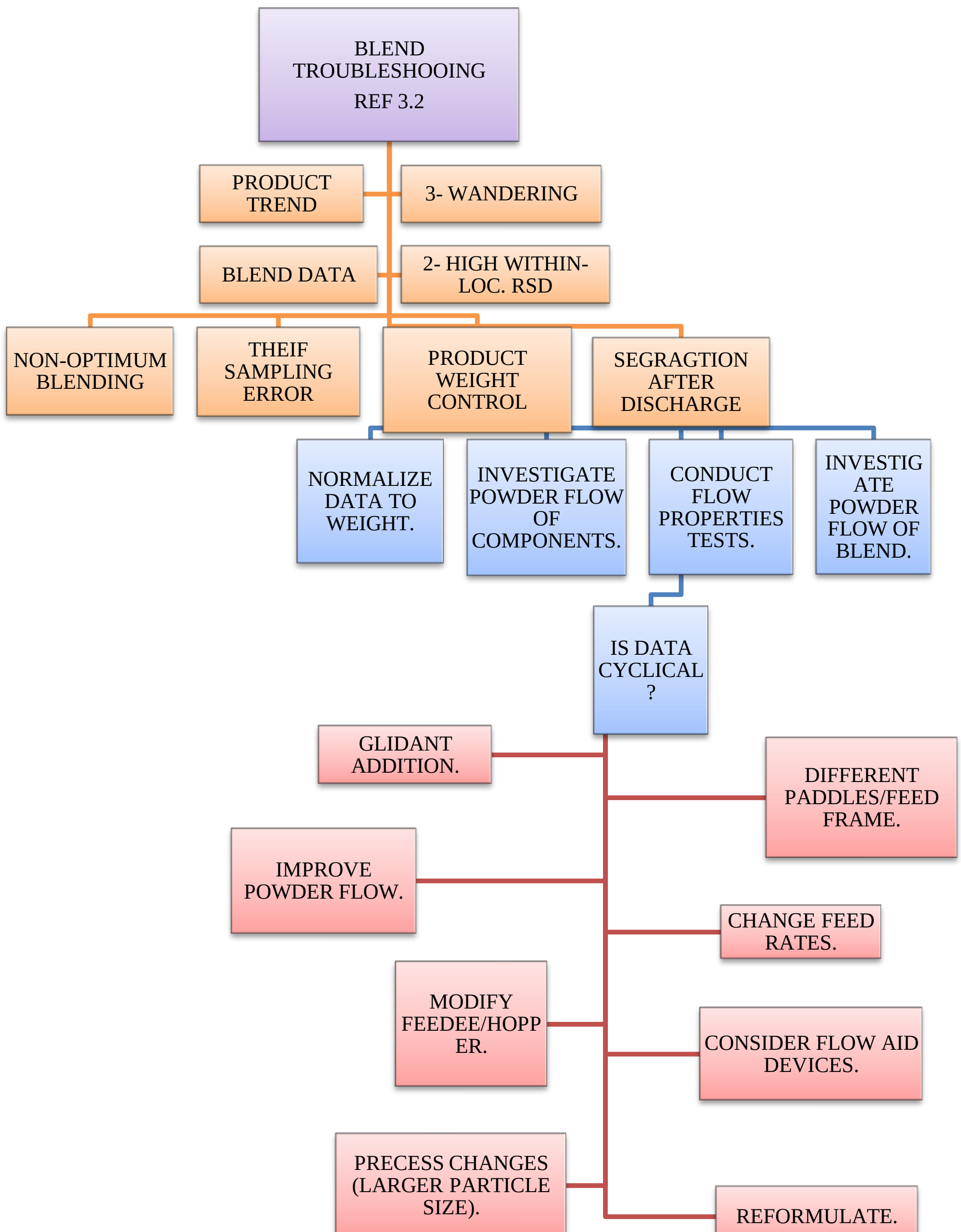


Figure 4.19: Decision tree REF. 3.3

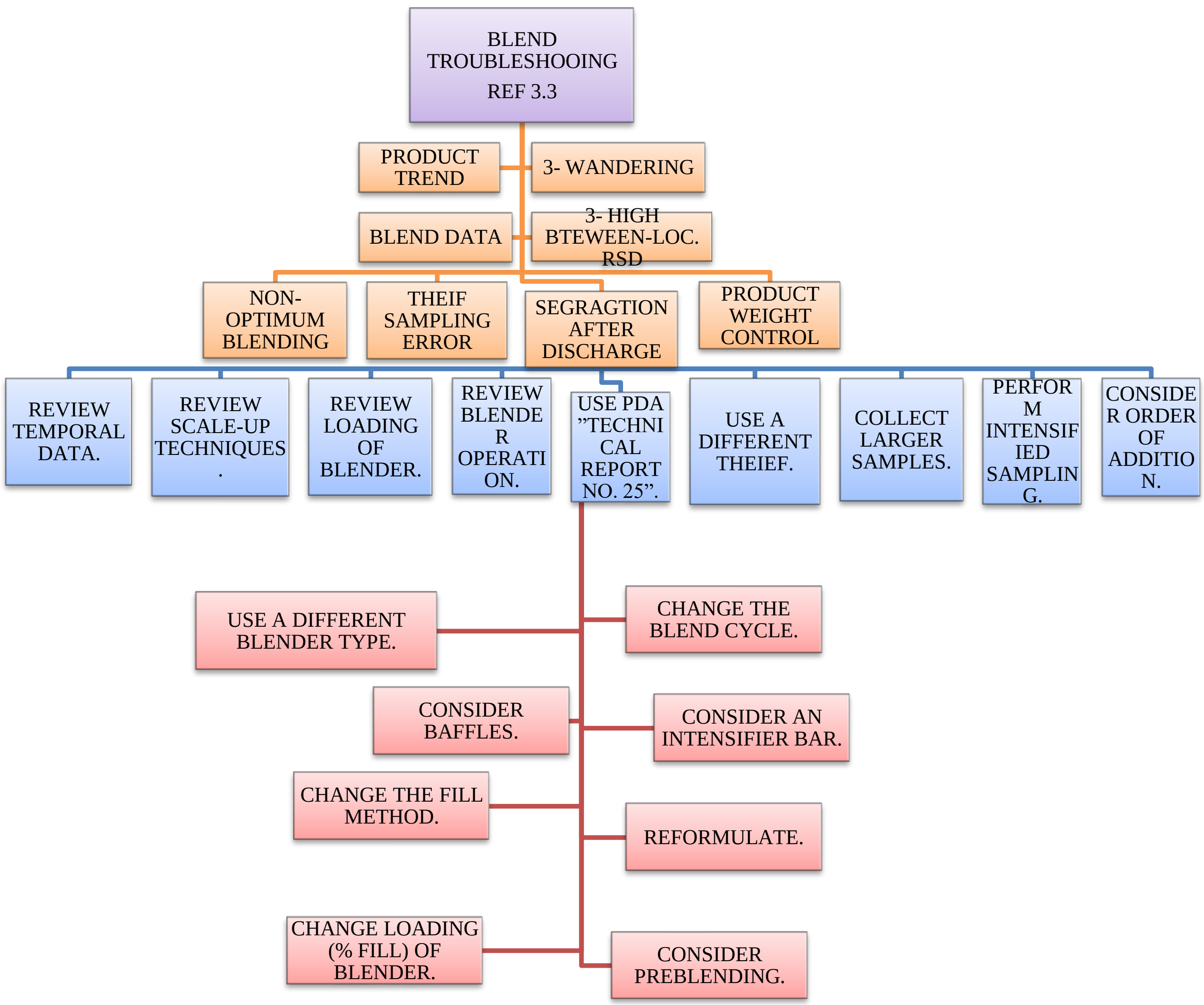


Figure 4.20: Decision tree REF. 3.4

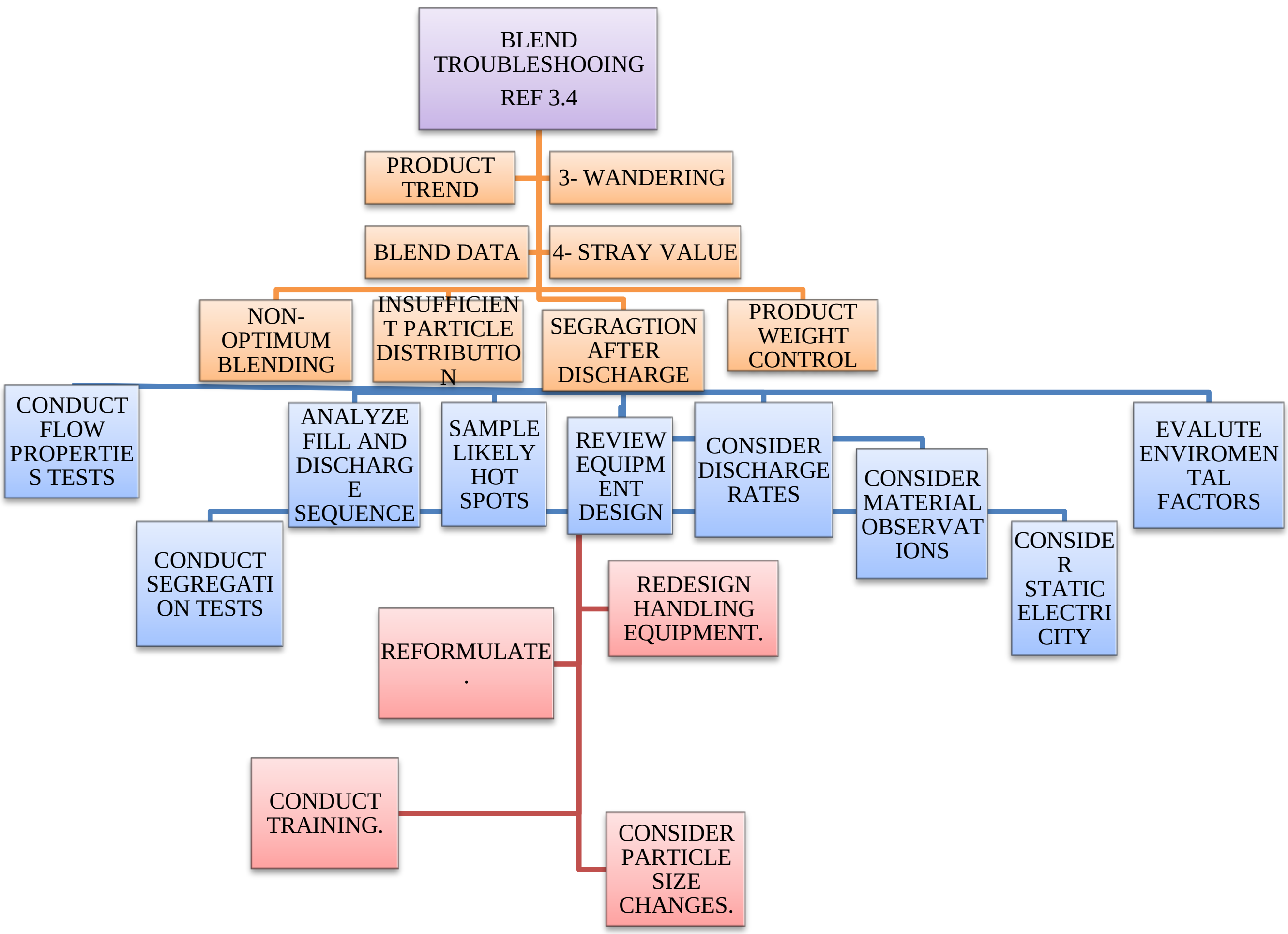


Figure 4.21: Decision tree REF. 3.5

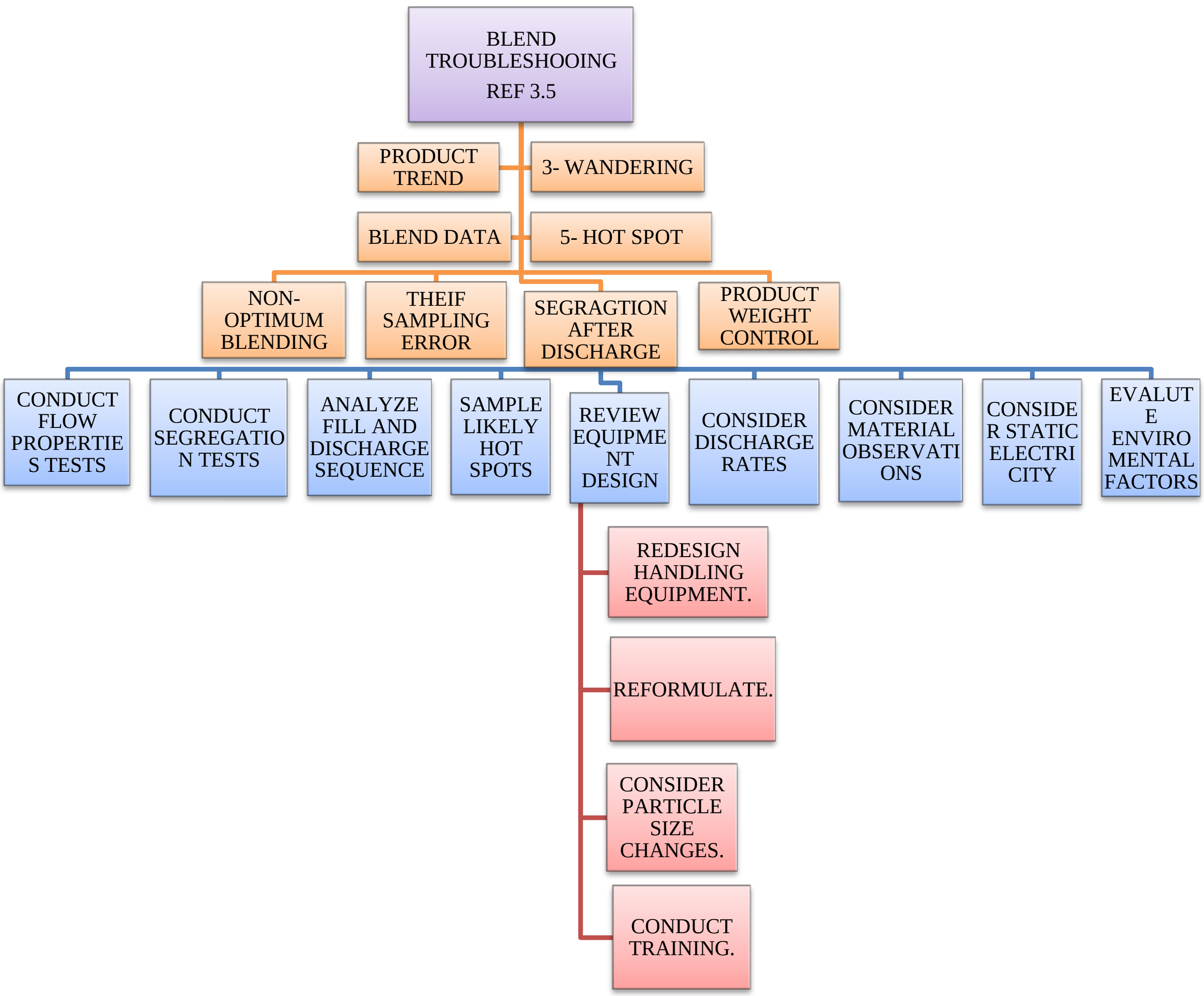


Figure 4.22: Decision tree REF. 3.6

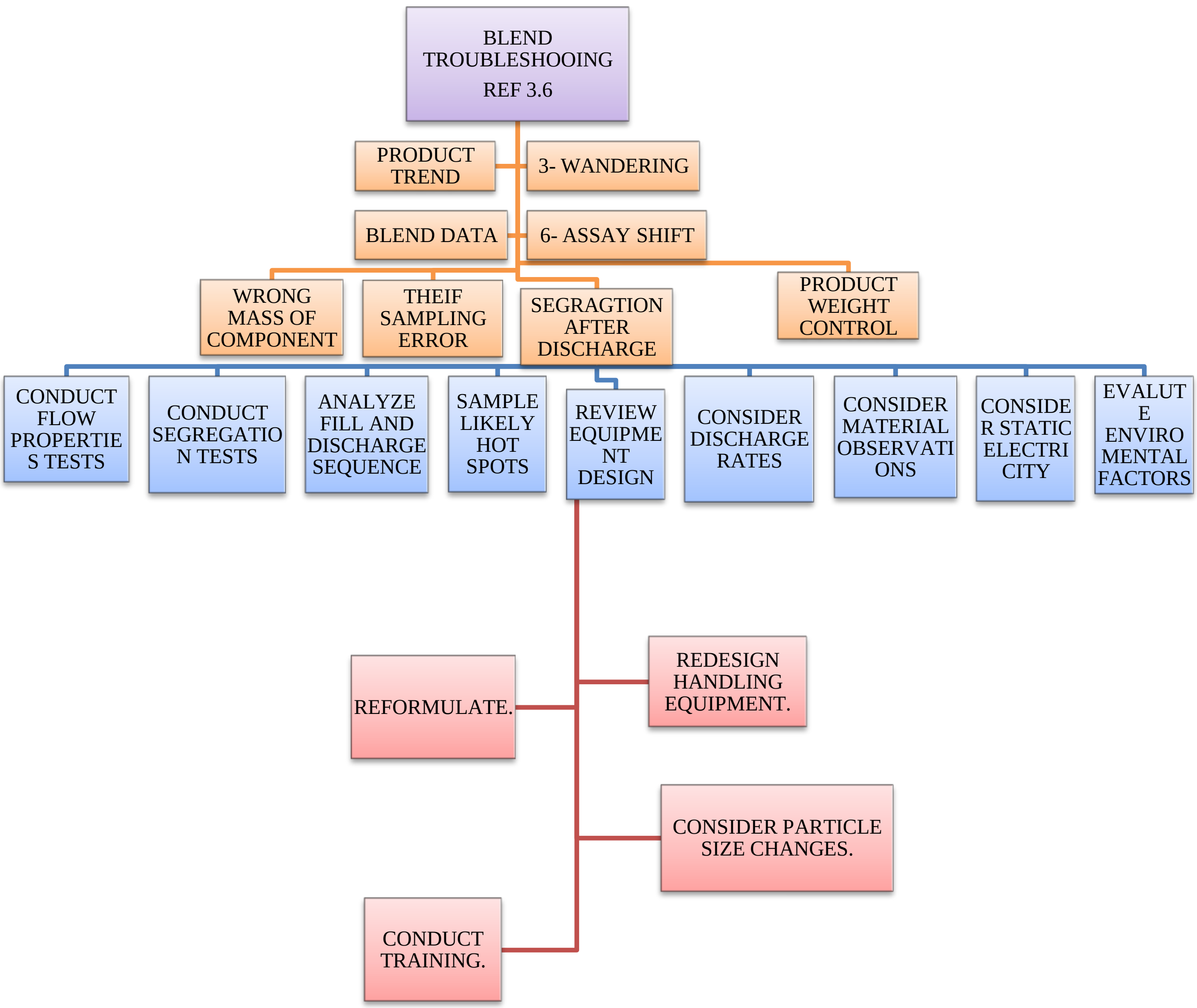


Figure 4.23: Decision tree REF. 3.0

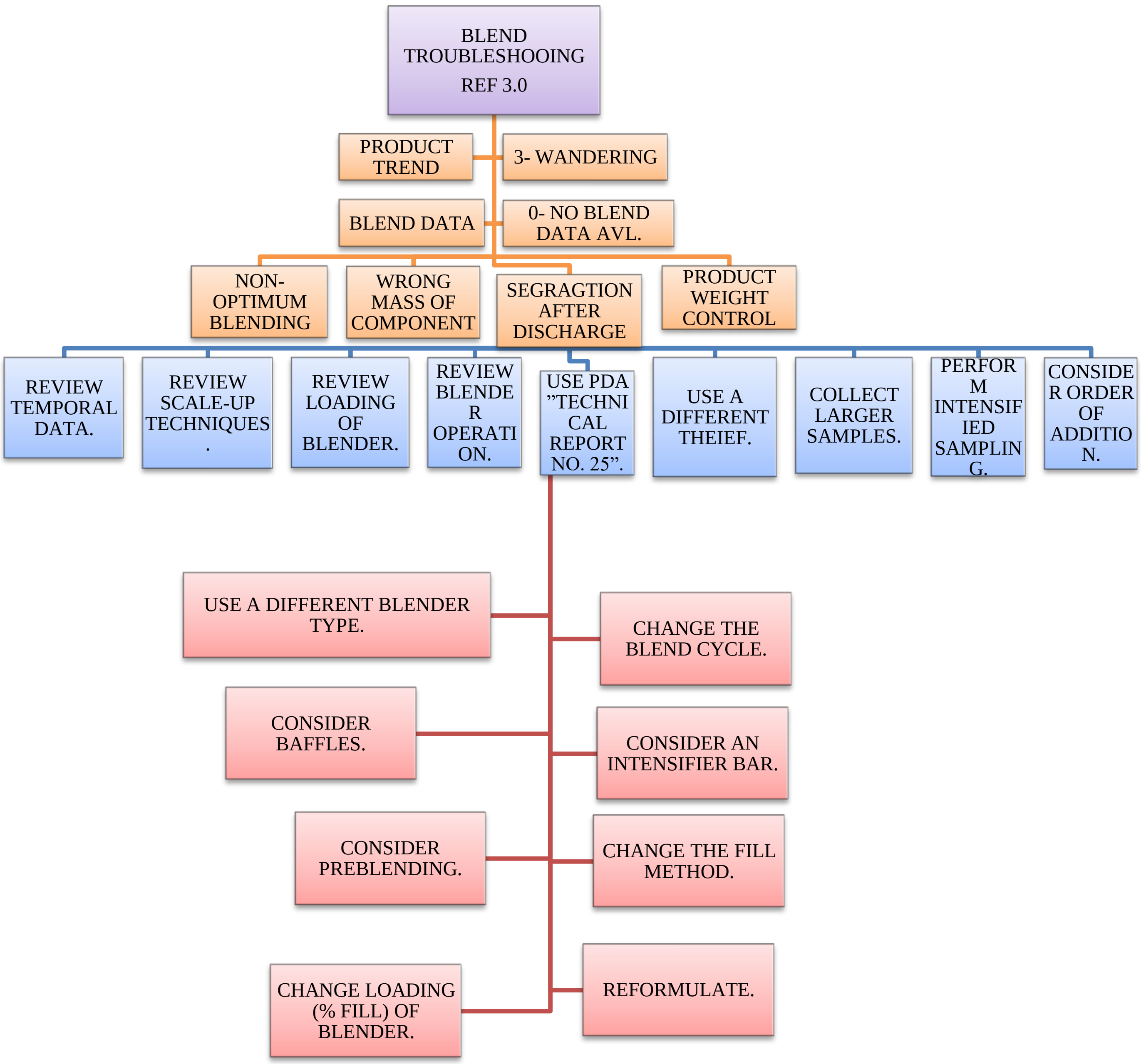


Figure 4.24: Decision tree REF. 4.1

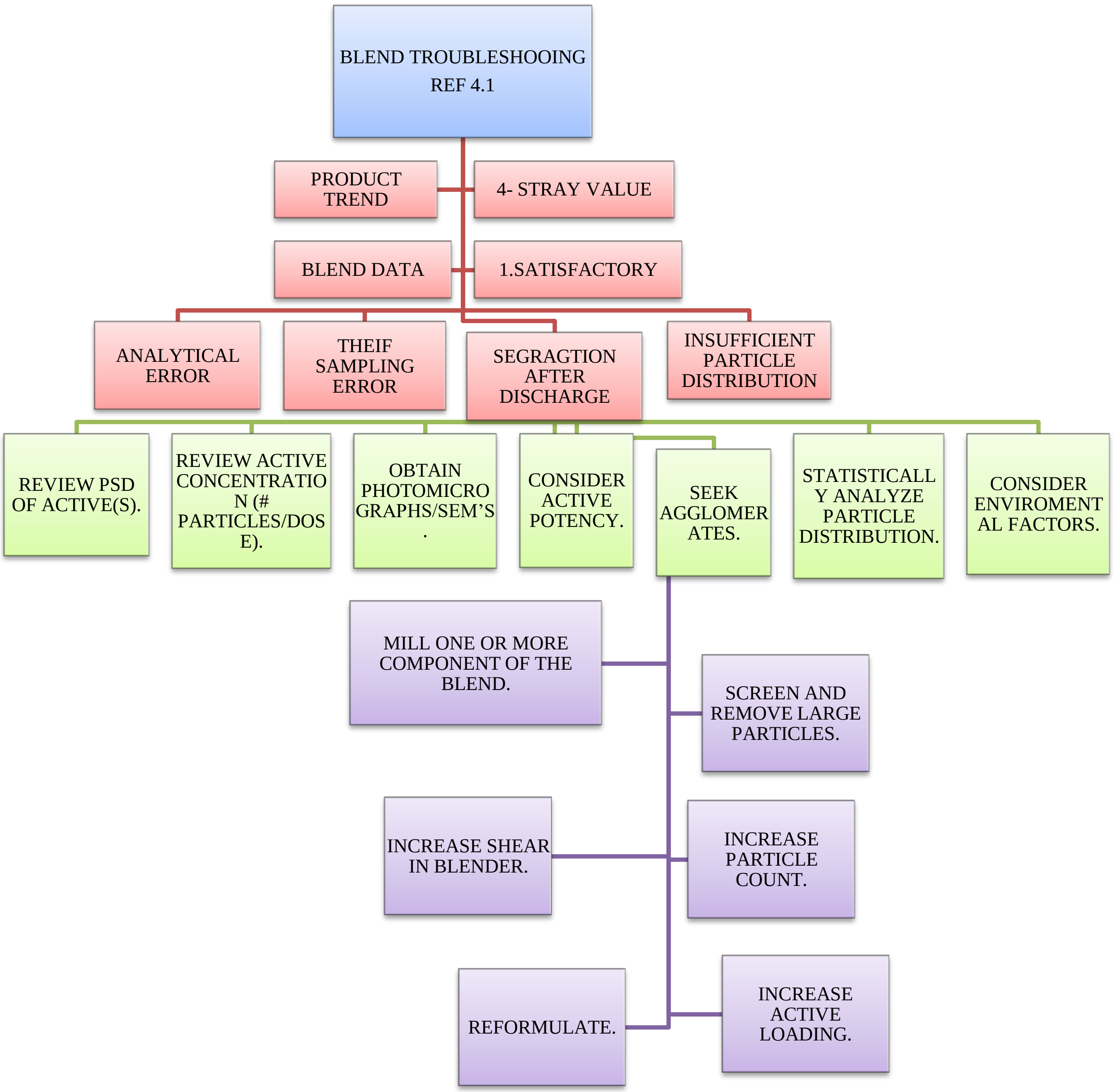


Figure 4.25: Decision tree REF. 4.2

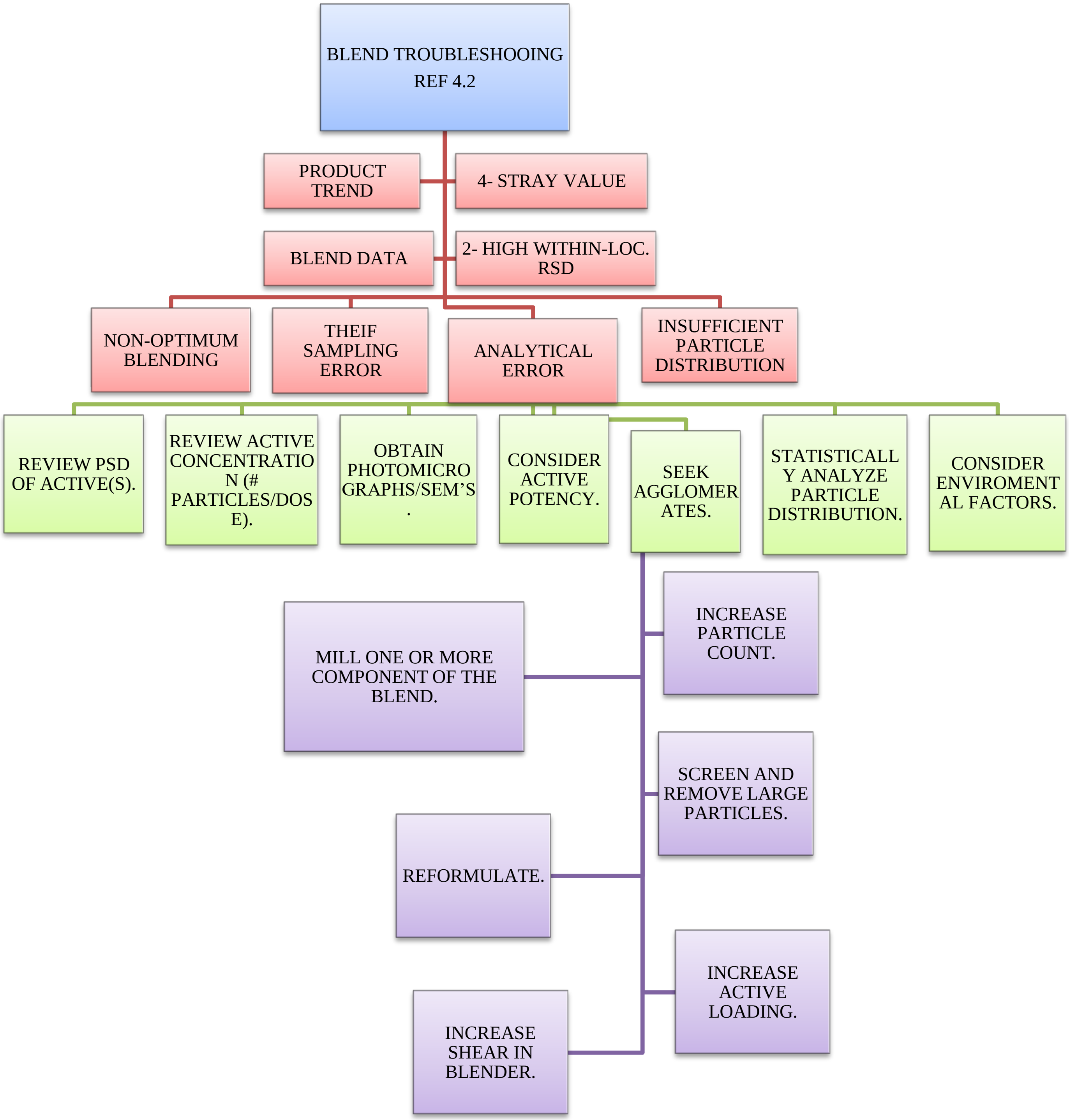


Figure 4.26: Decision tree REF. 4.3

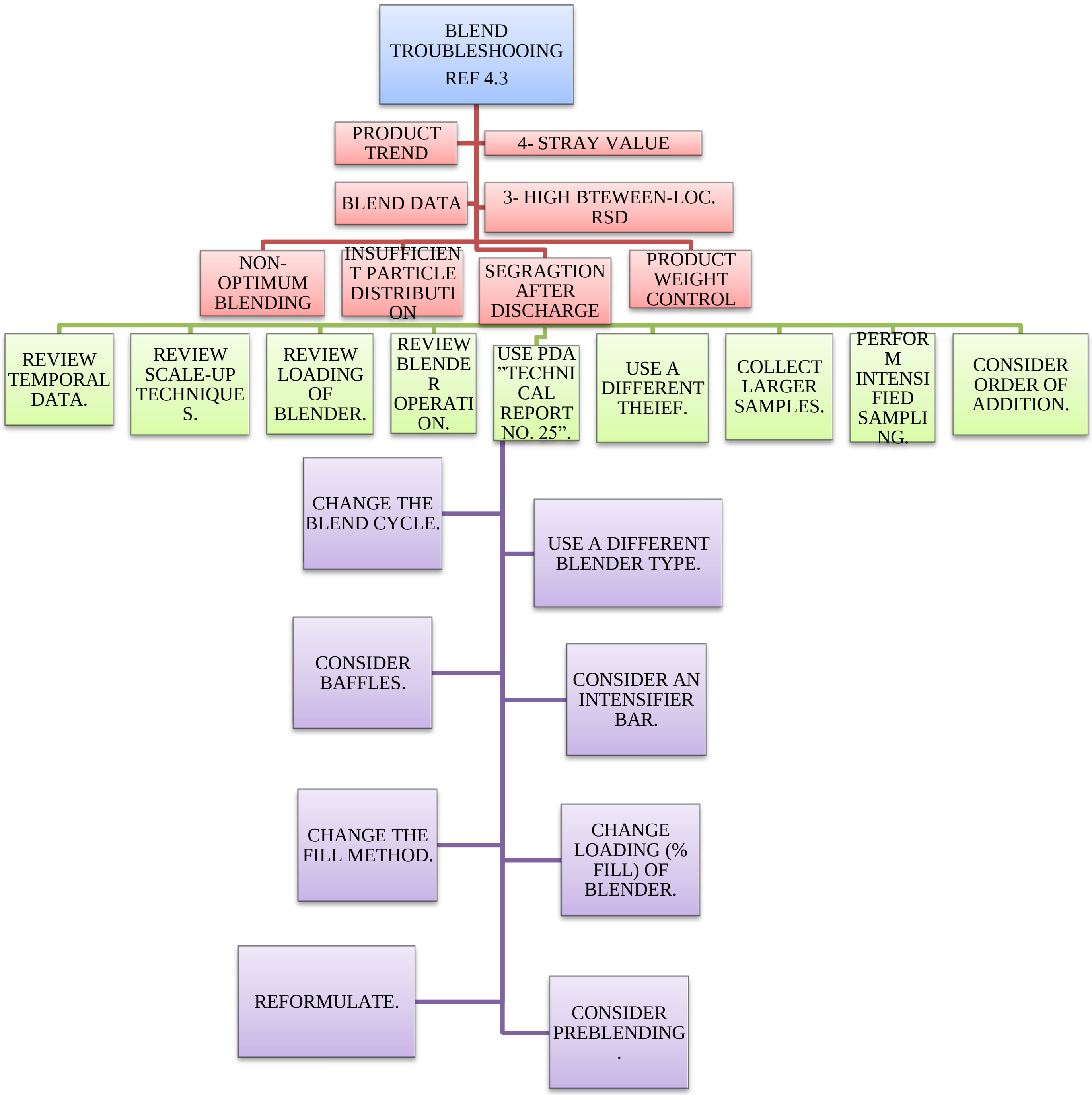


Figure 4.27: Decision tree REF. 4.4

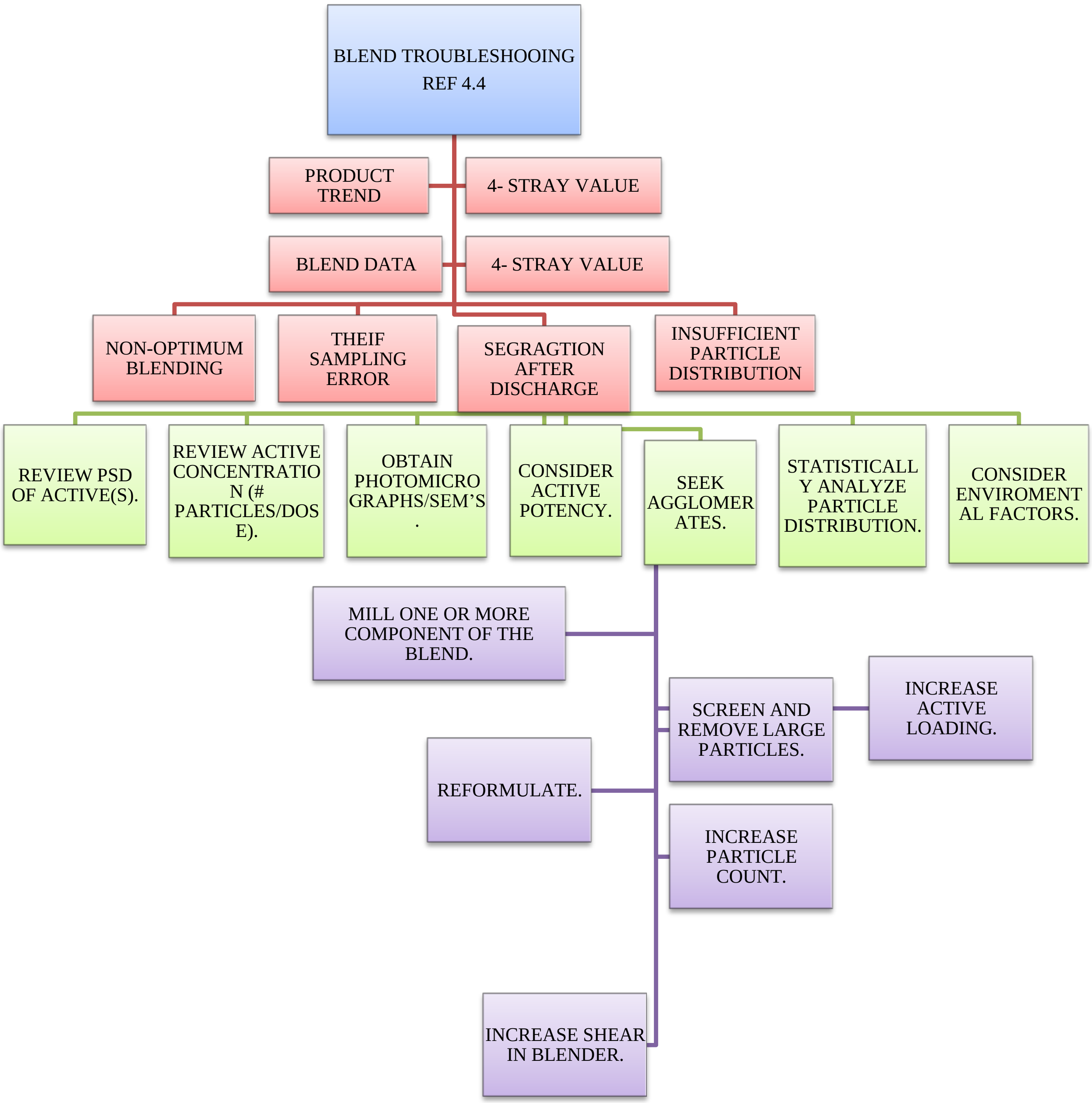


Figure 4.28: Decision tree REF. 4.5

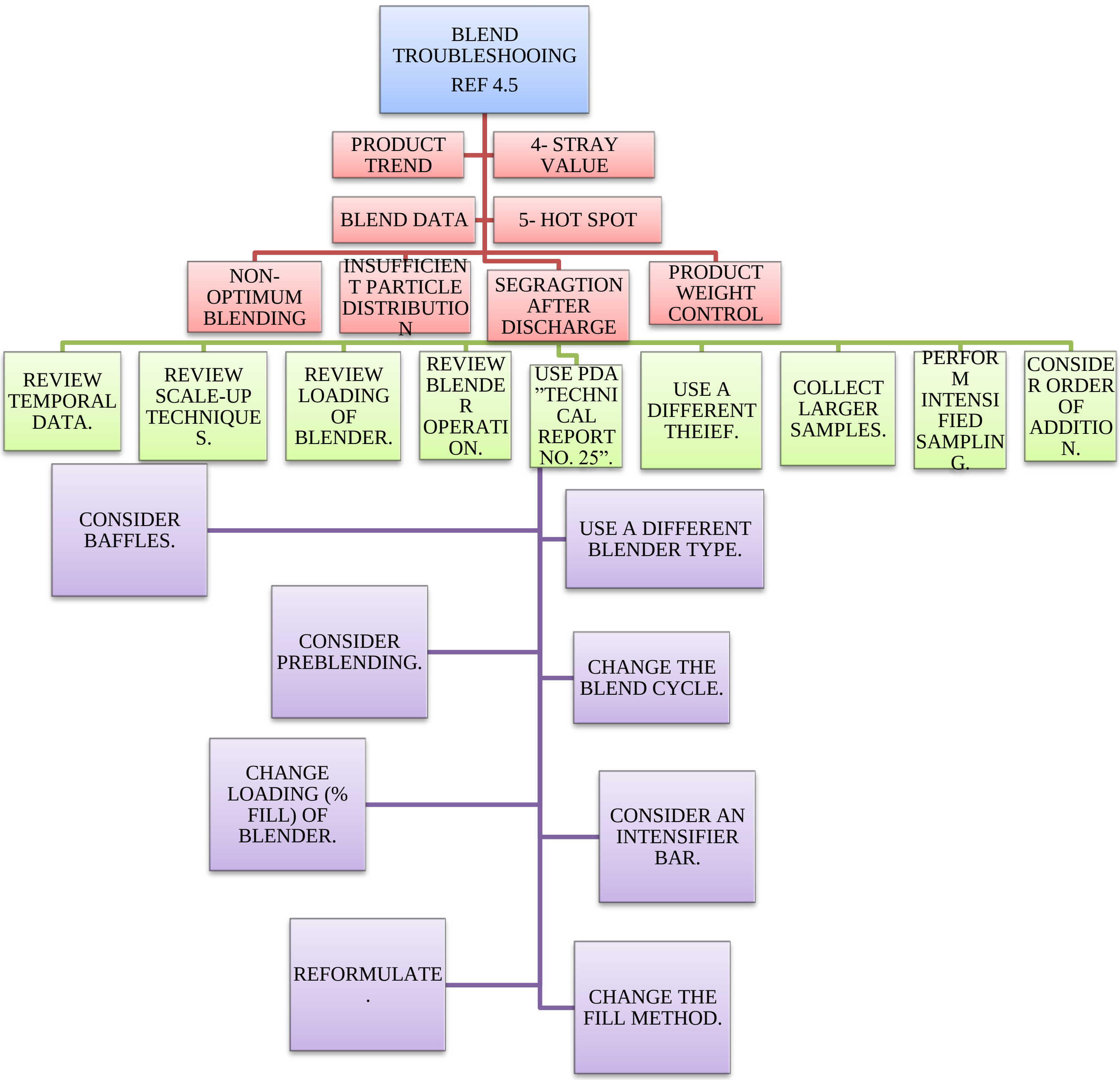


Figure 4.29: Decision tree REF. 4.6

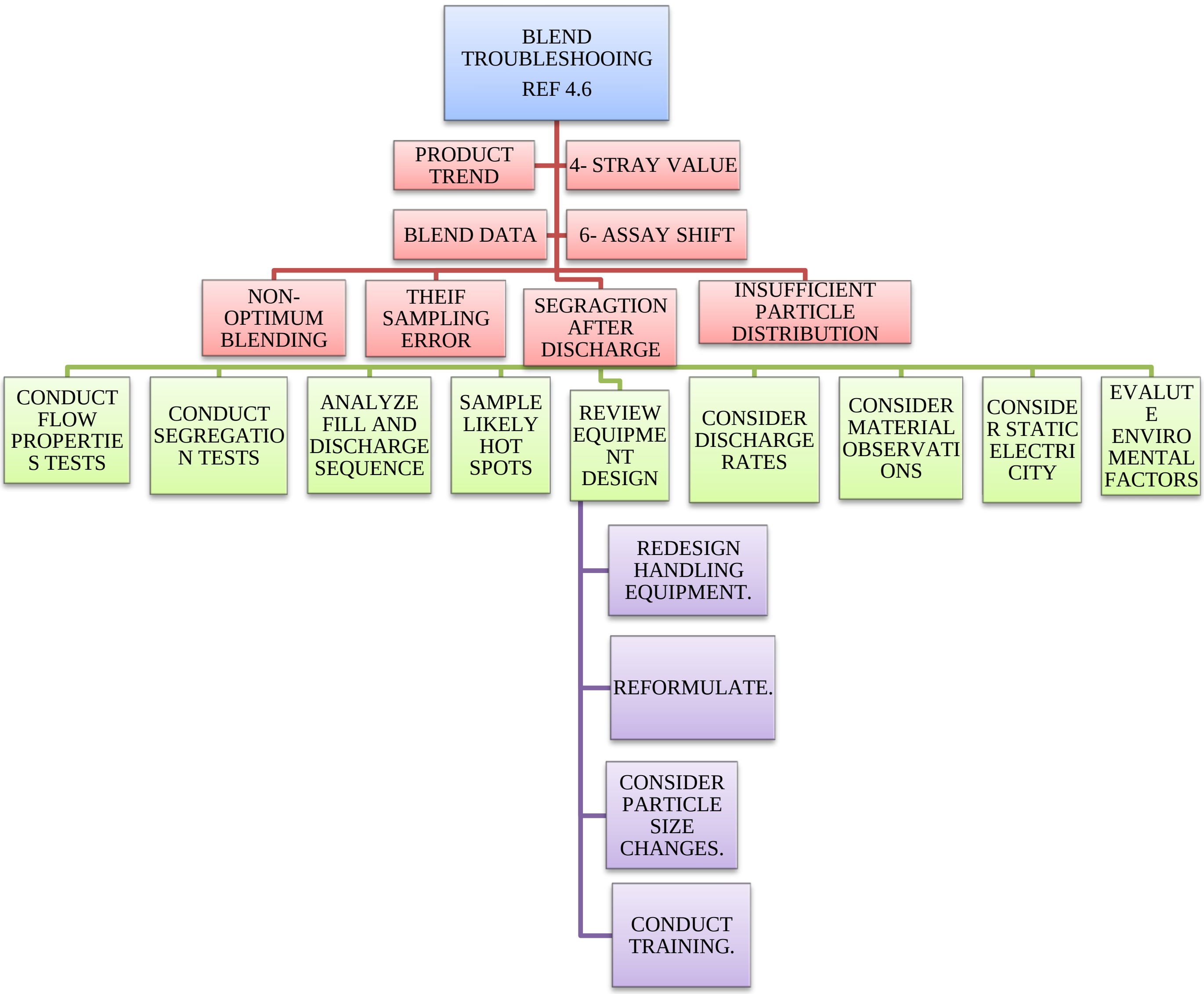


Figure 4.30: Decision tree REF. 4.0

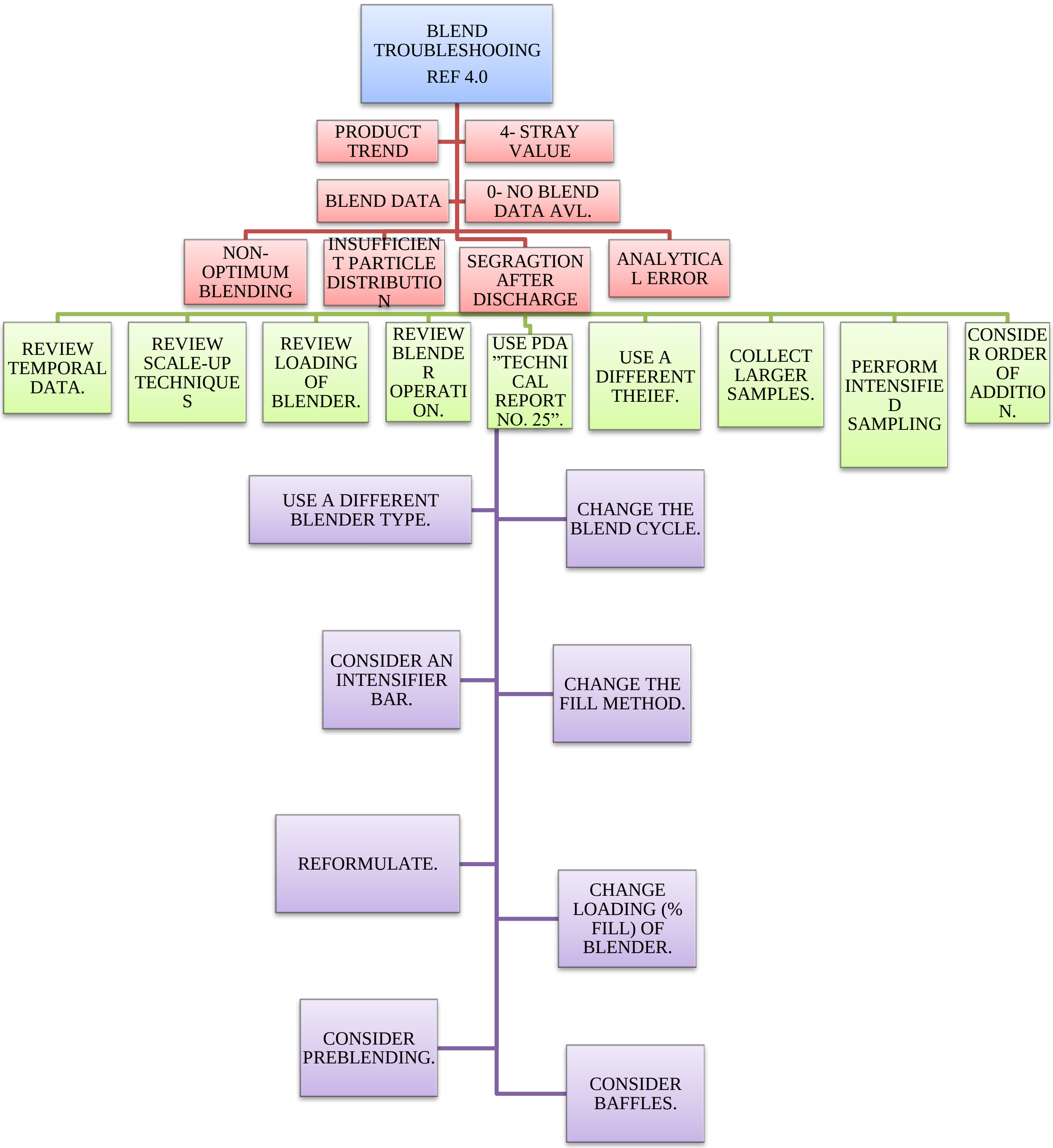


Figure 4.31: Decision tree REF. 5.1

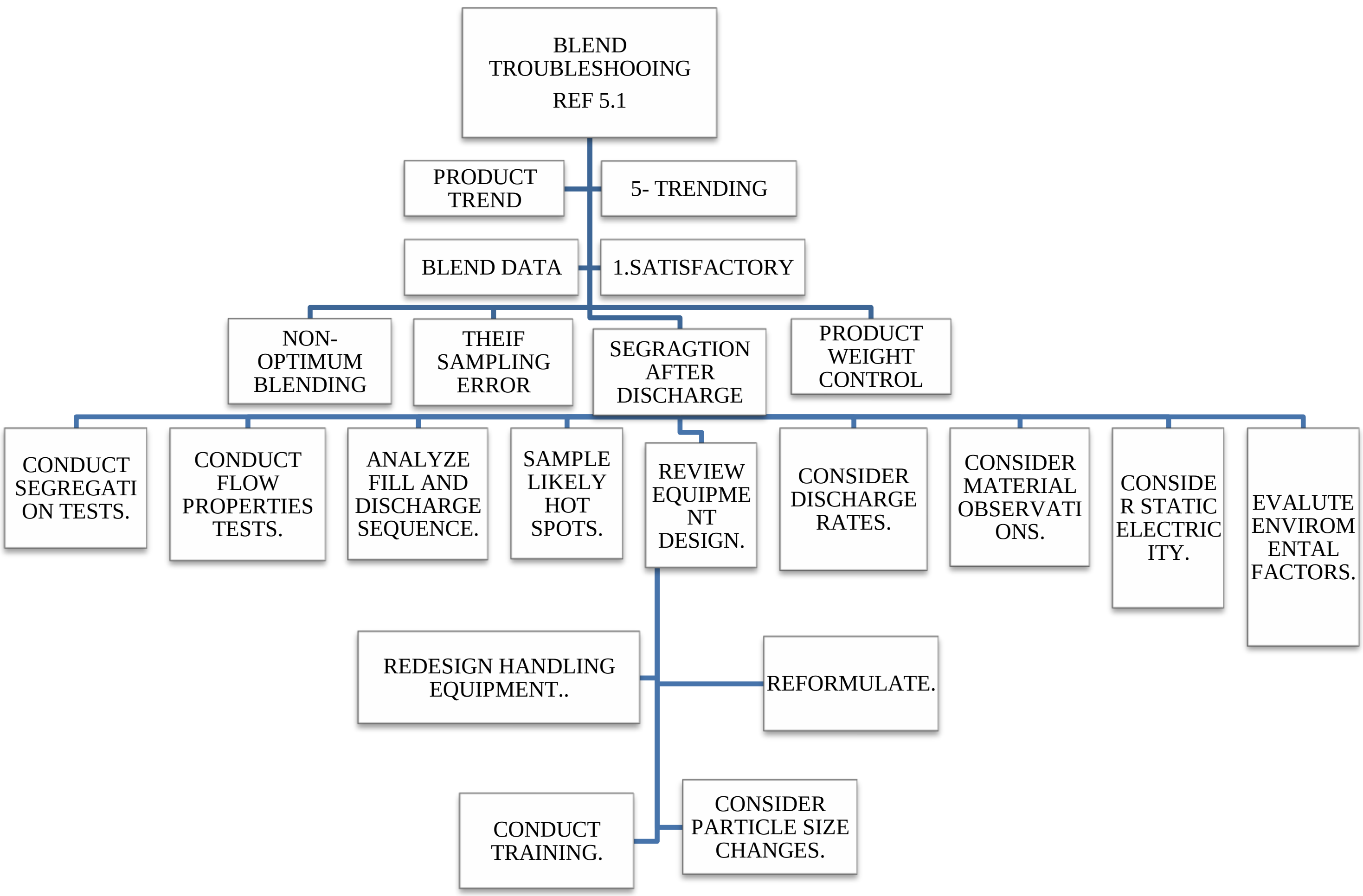


Figure 4.32: Decision tree REF. 5.2

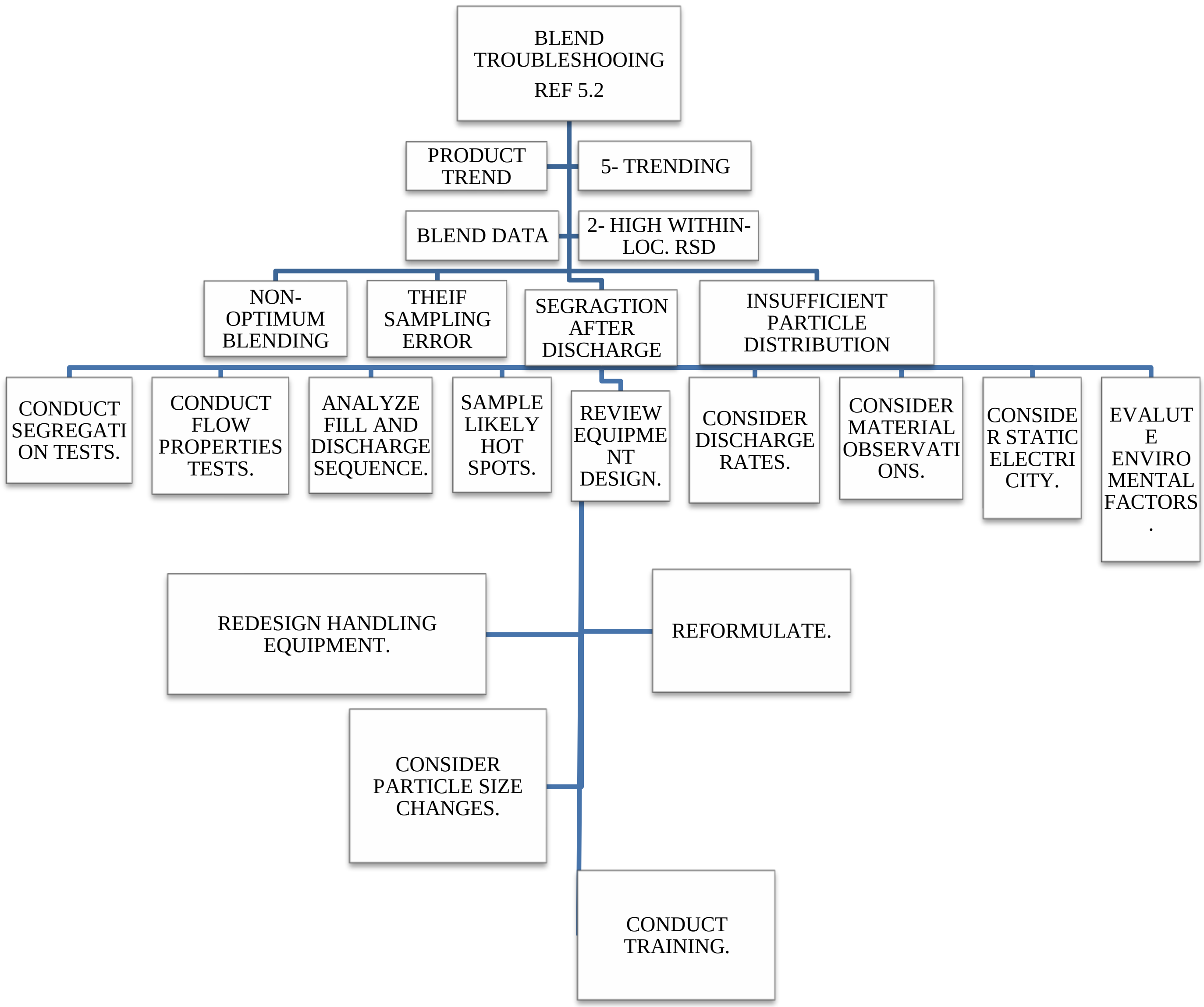


Figure 4.33: Decision tree REF. 5.3

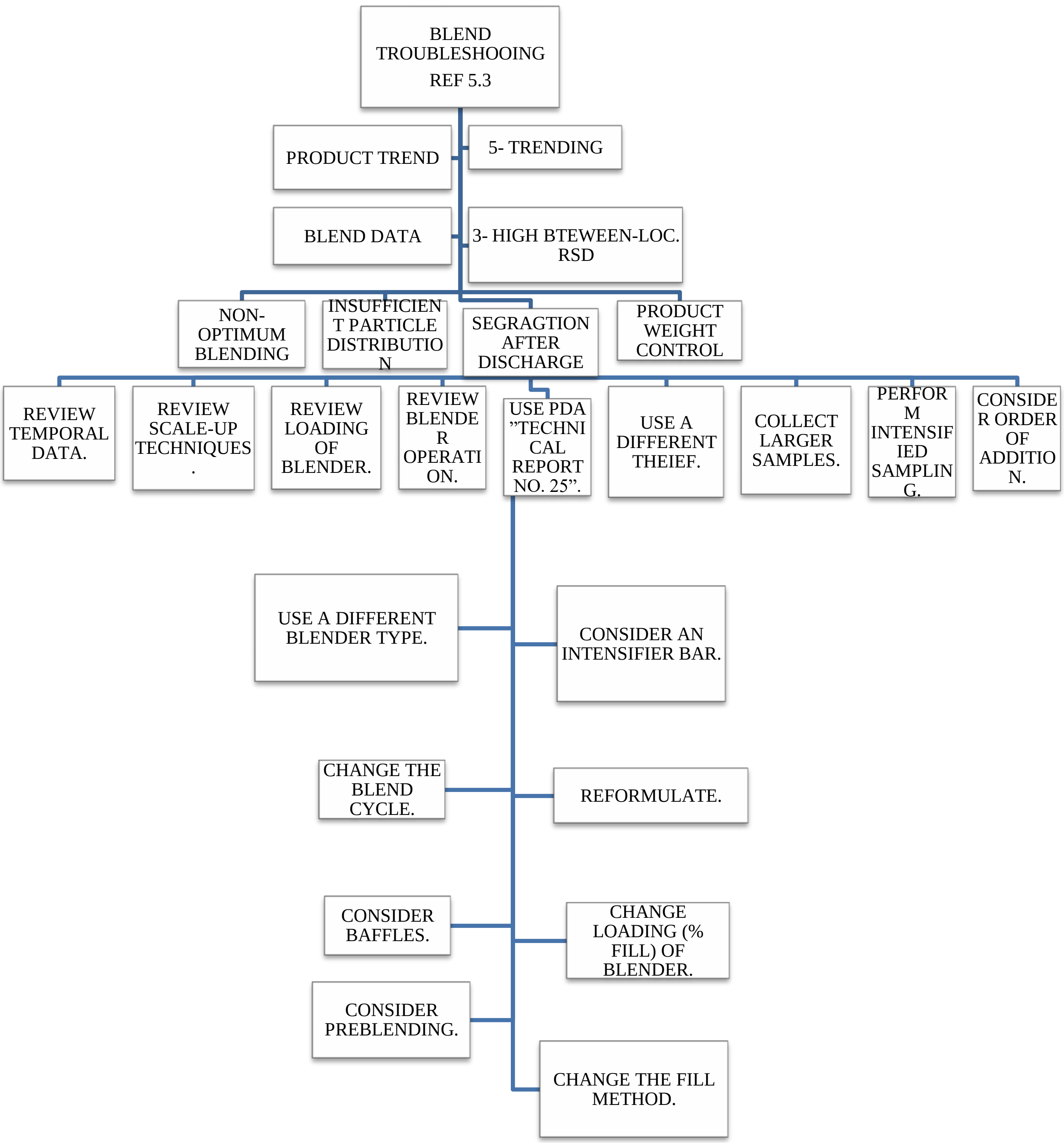


Figure 4.34: Decision tree REF. 5.4

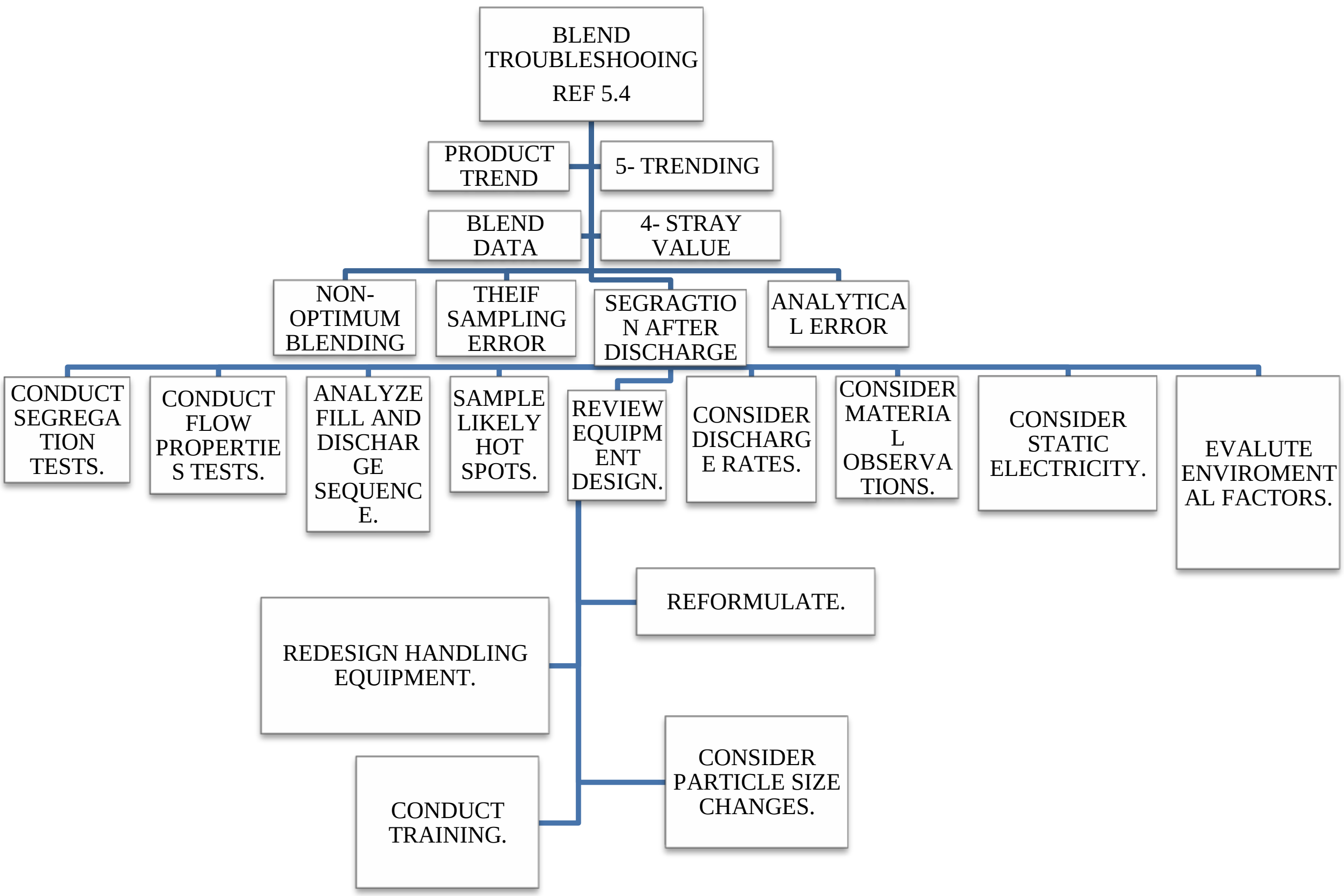


Figure 4.35: Decision tree REF. 5.5

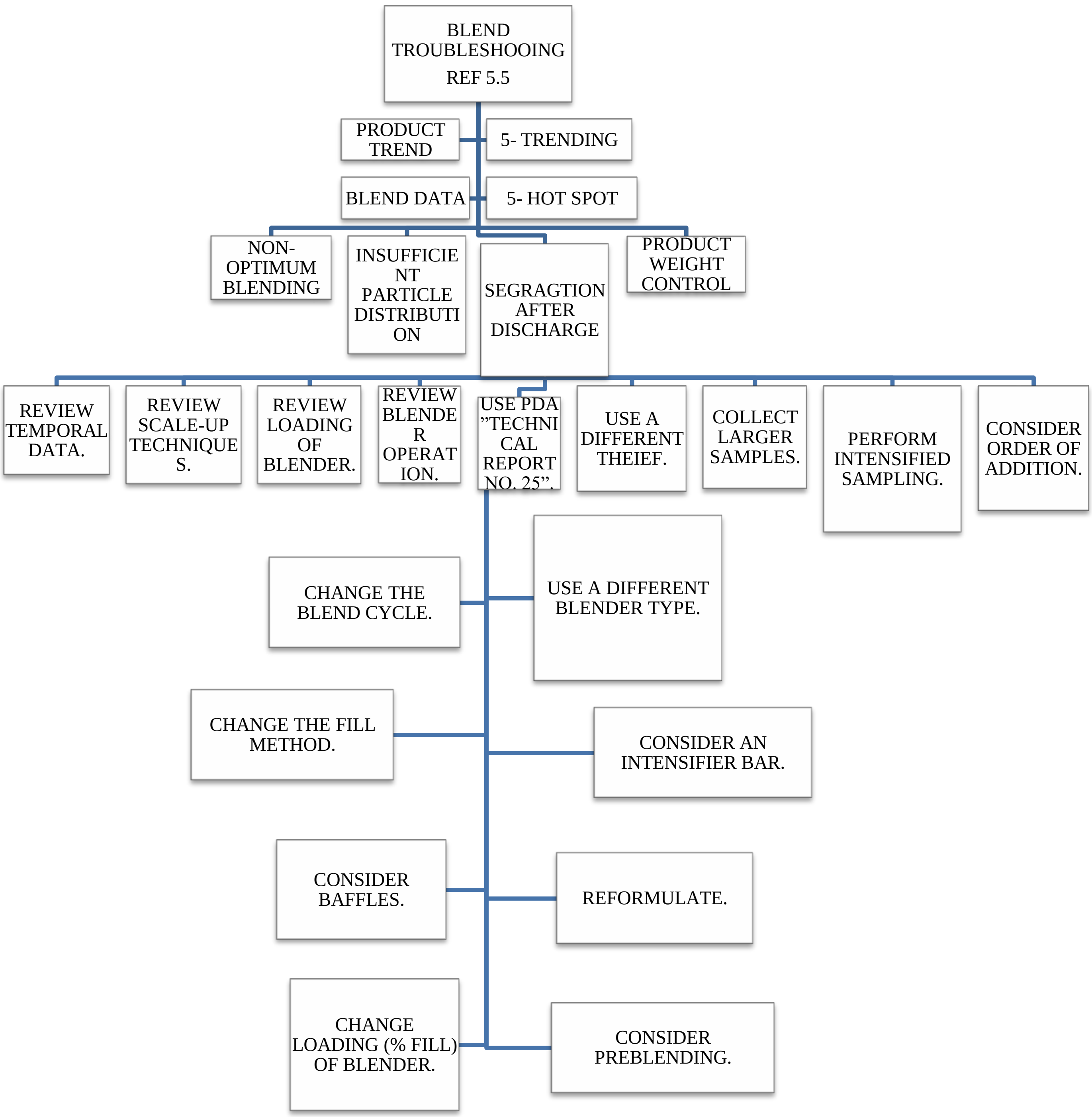


Figure 4.36: Decision tree REF. 5.6

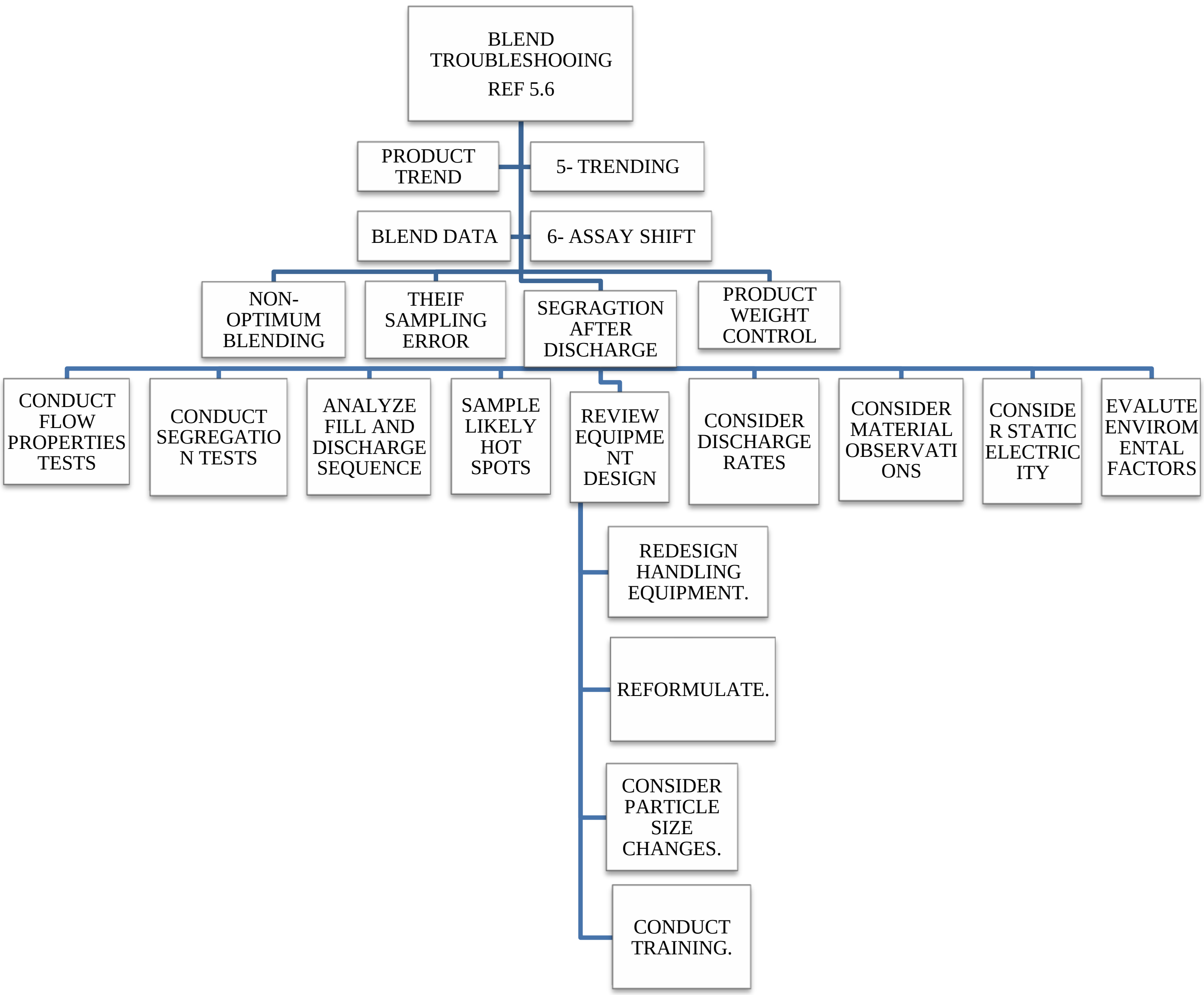


Figure 4.37: Decision tree REF. 5.0

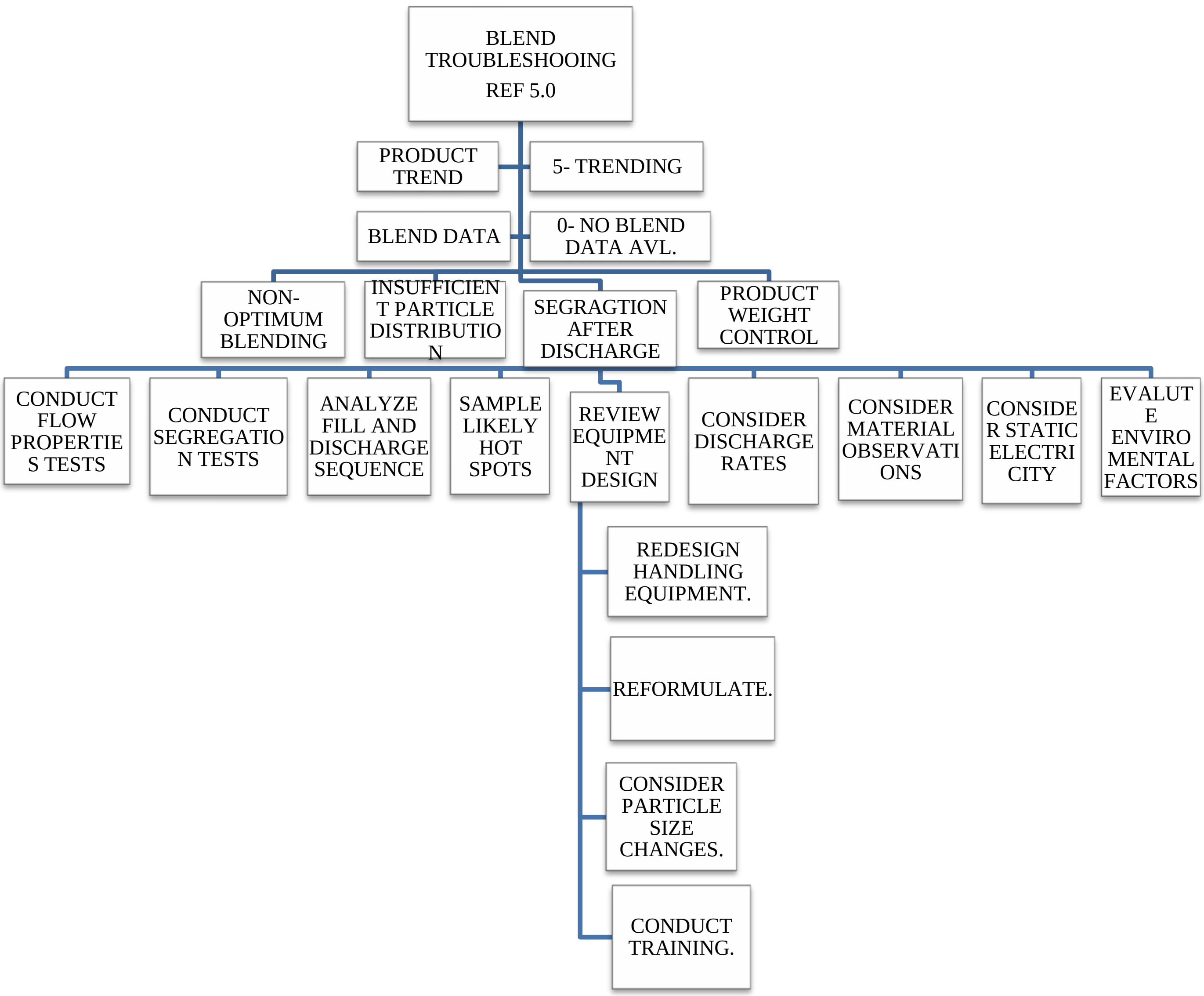


Figure 4.38: Decision tree REF. 6.1

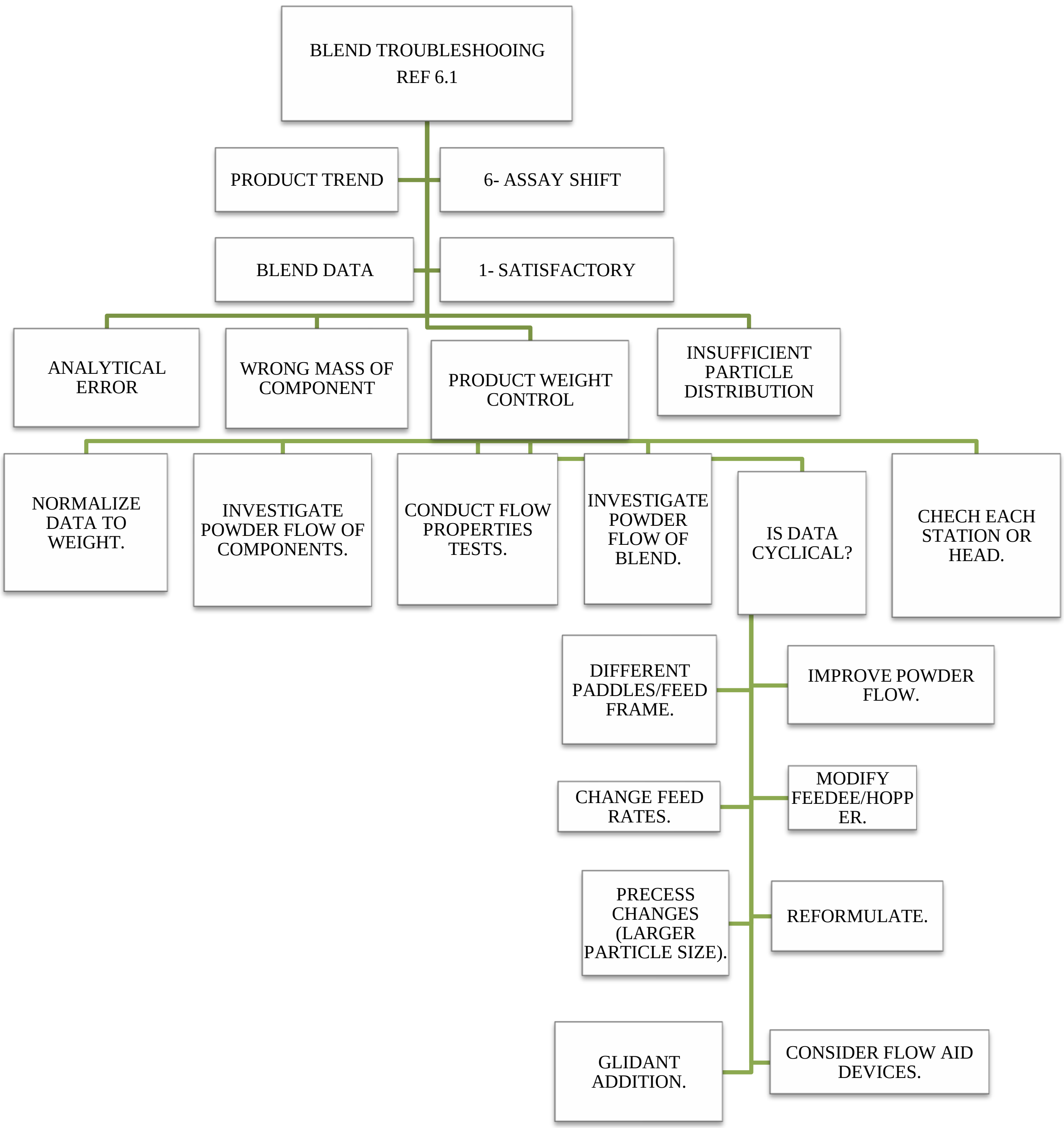


Figure 4.39: Decision tree REF. 6.2

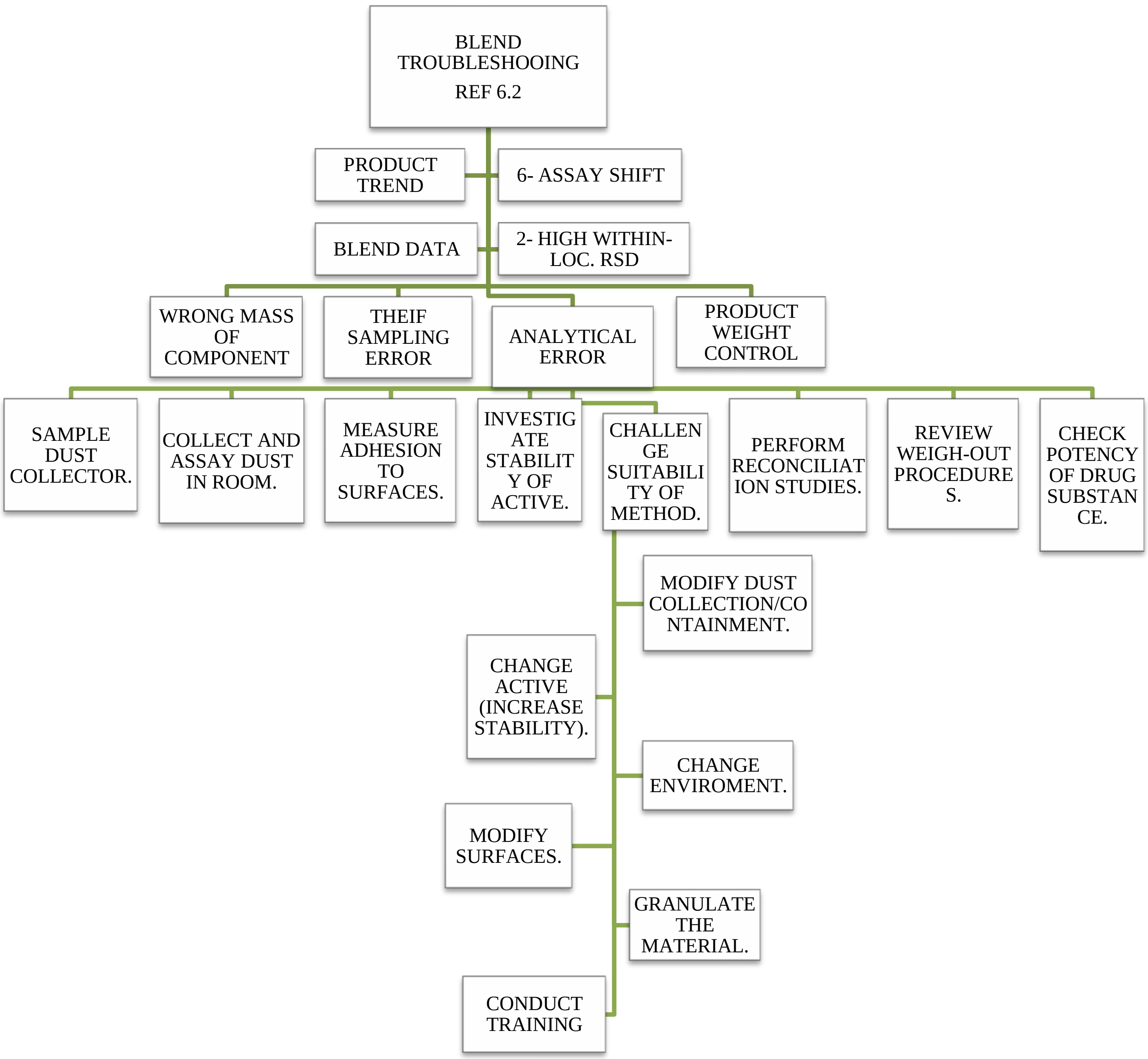


Figure 4.40: Decision tree REF. 6.3

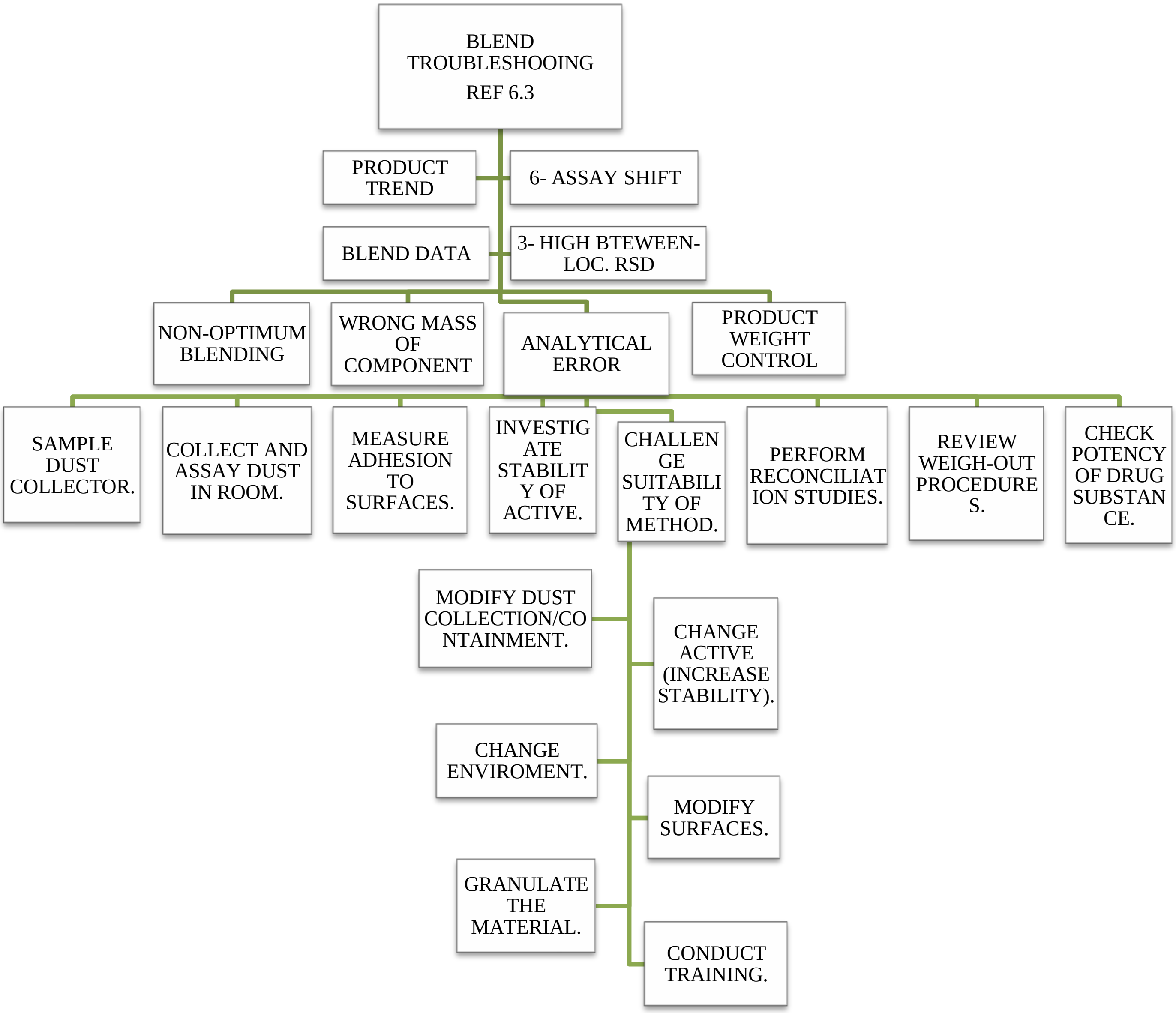


Figure 4.41: Decision tree REF. 6.4

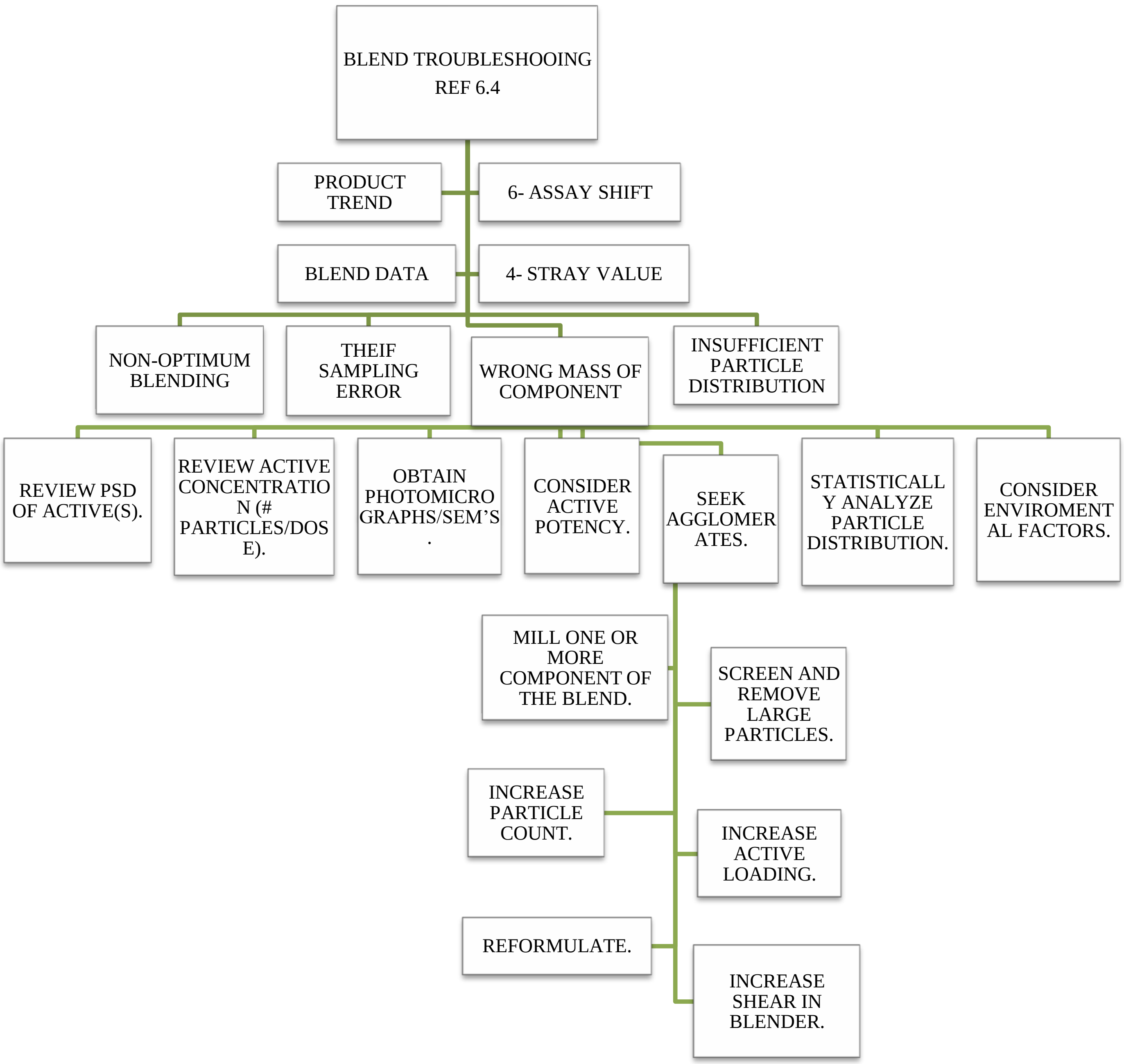


Figure 4.42: Decision tree REF. 6.5

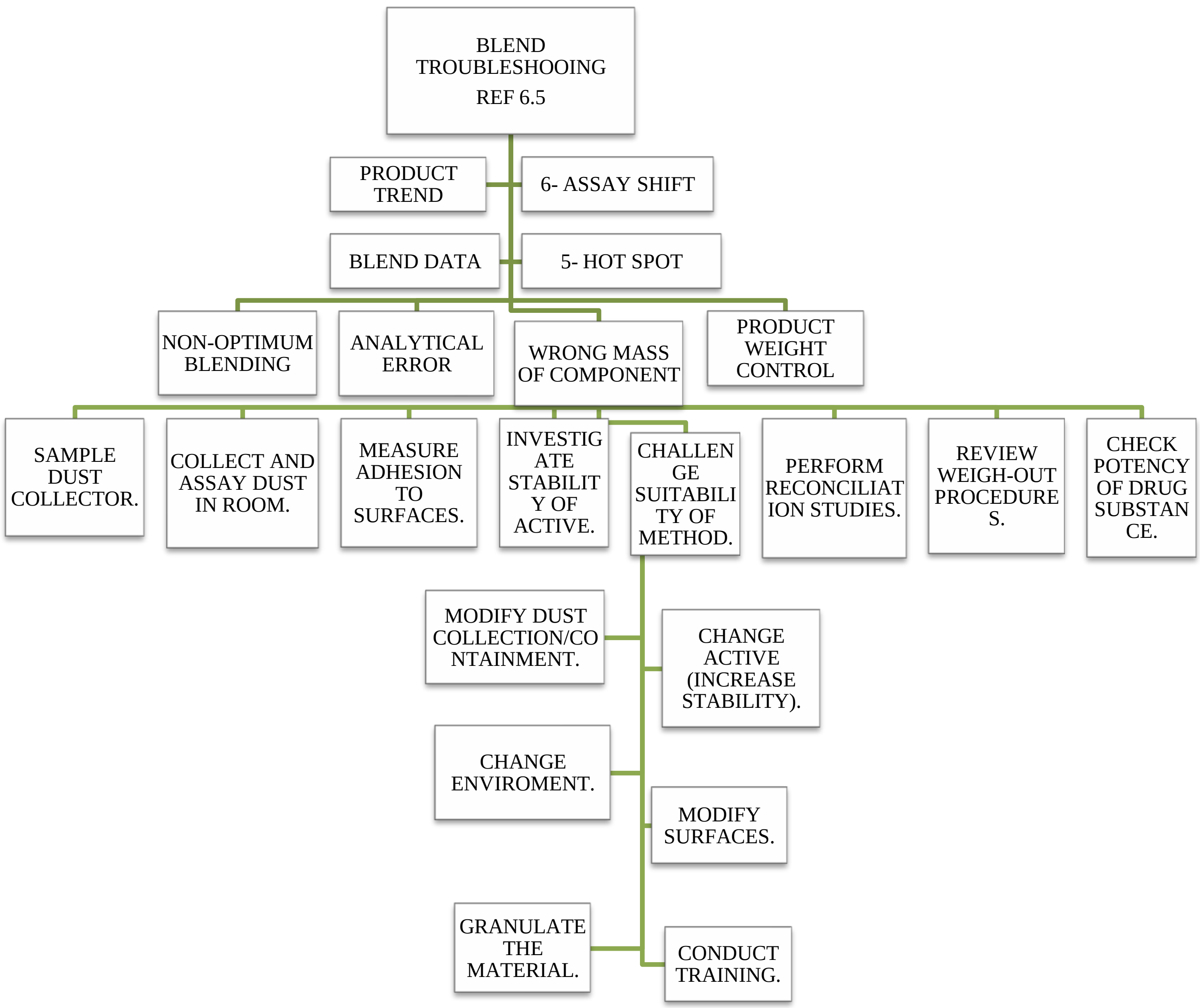


Figure 4.43: Decision tree REF. 6.6

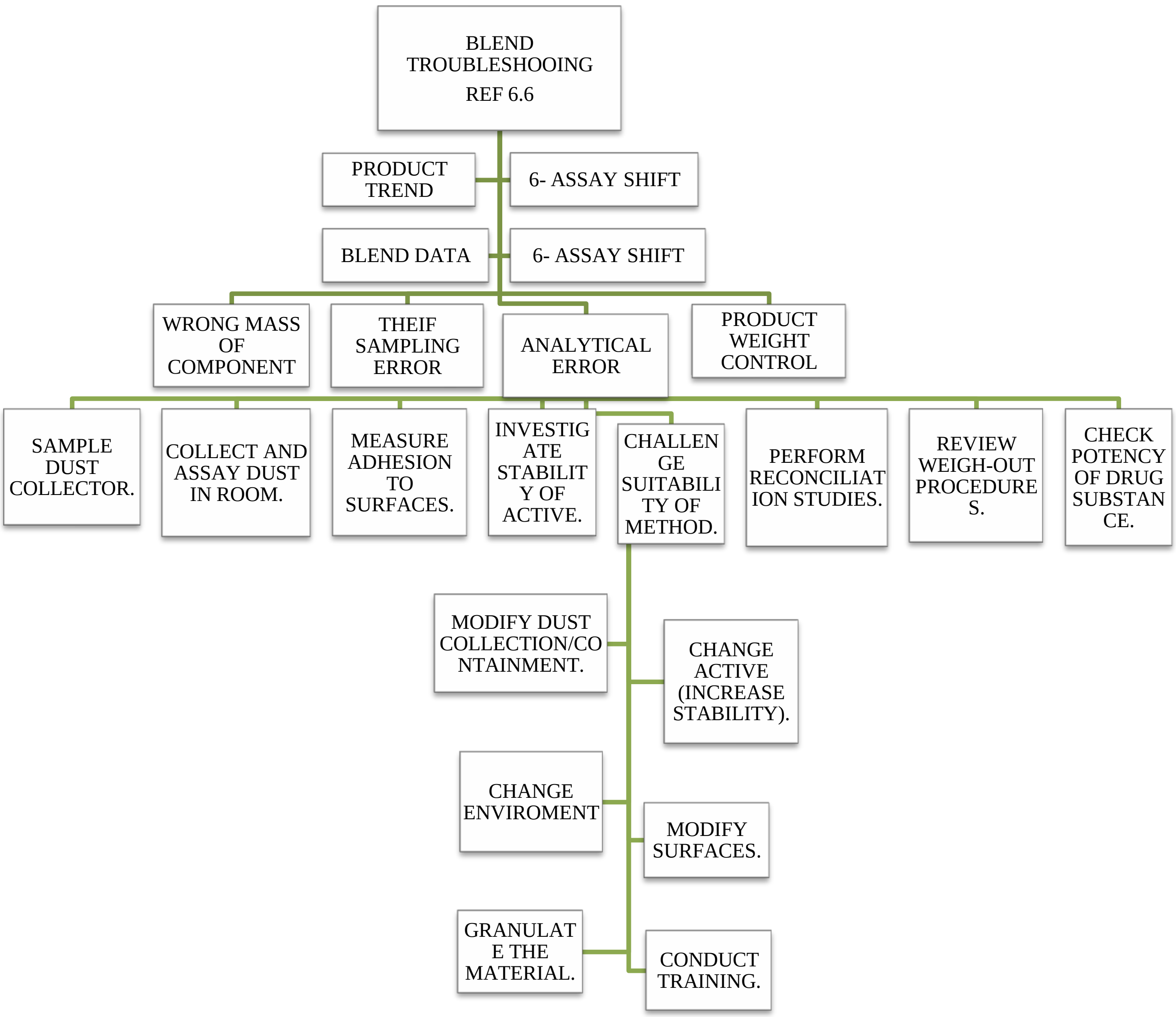


Figure 4.44: Decision tree REF. 6.0

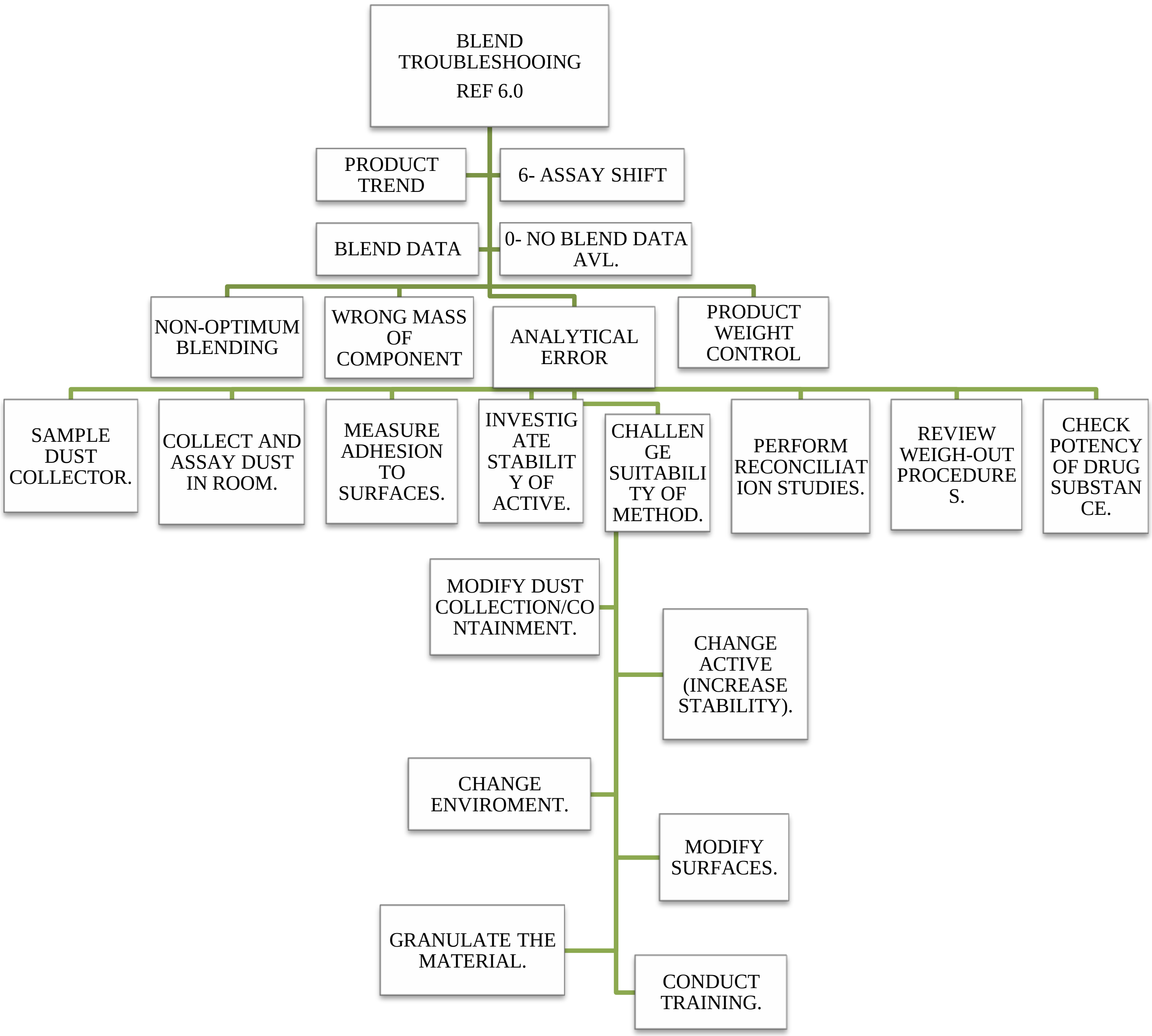


Figure 4.45: Decision tree REF. 0.1

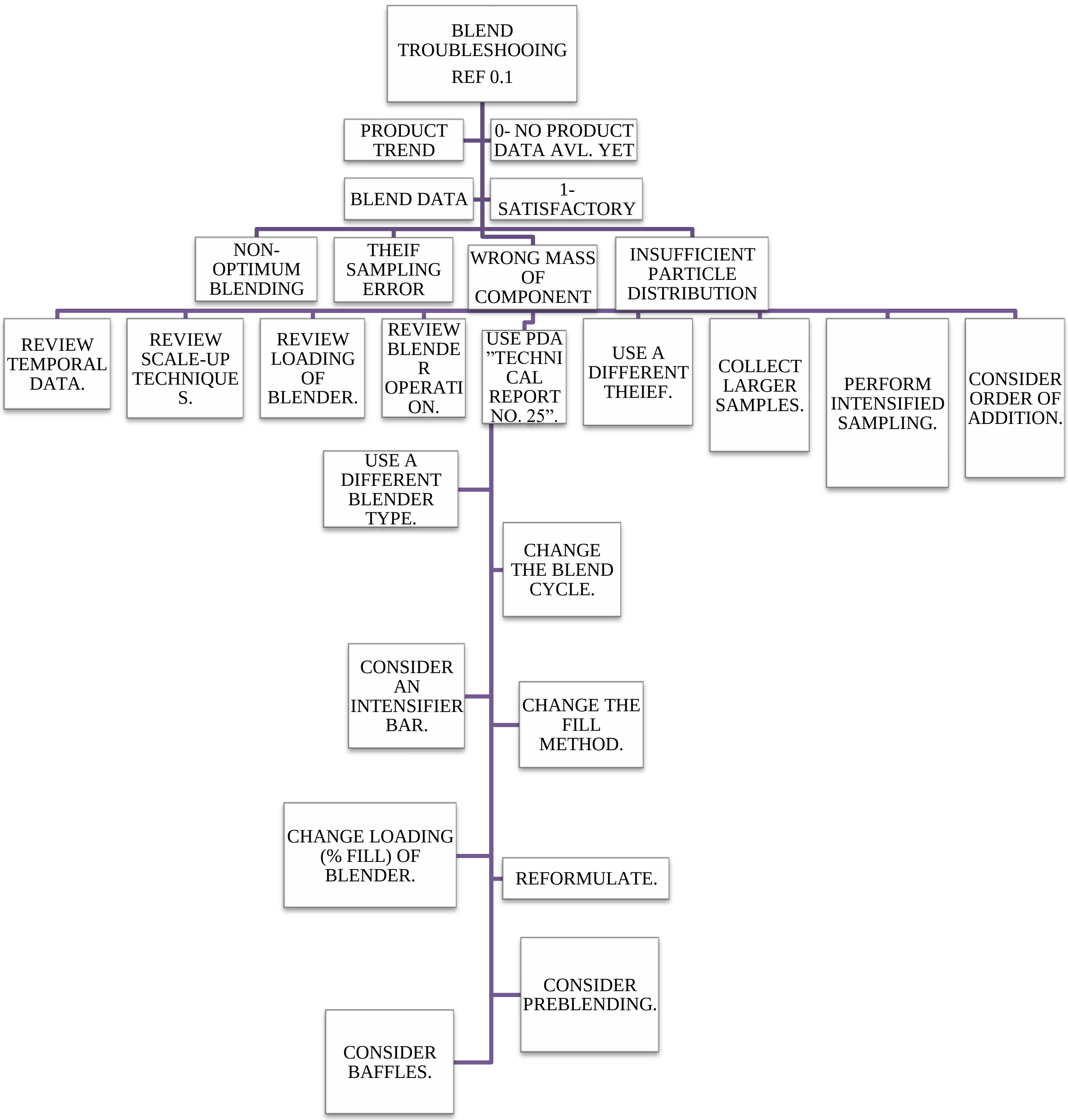


Figure 4.46: Decision tree REF. 0.2

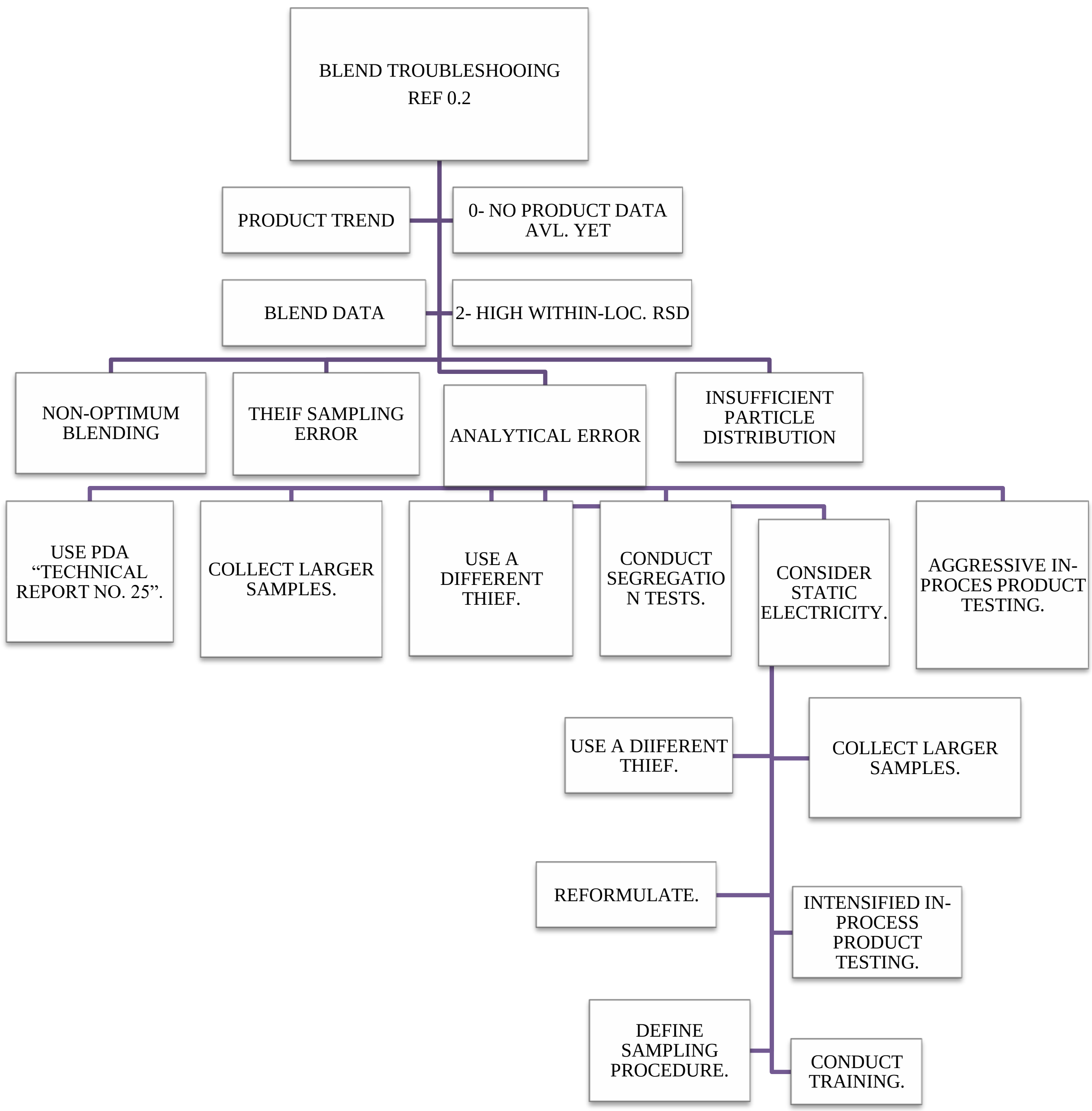


Figure 4.47: Decision tree REF. 0.3

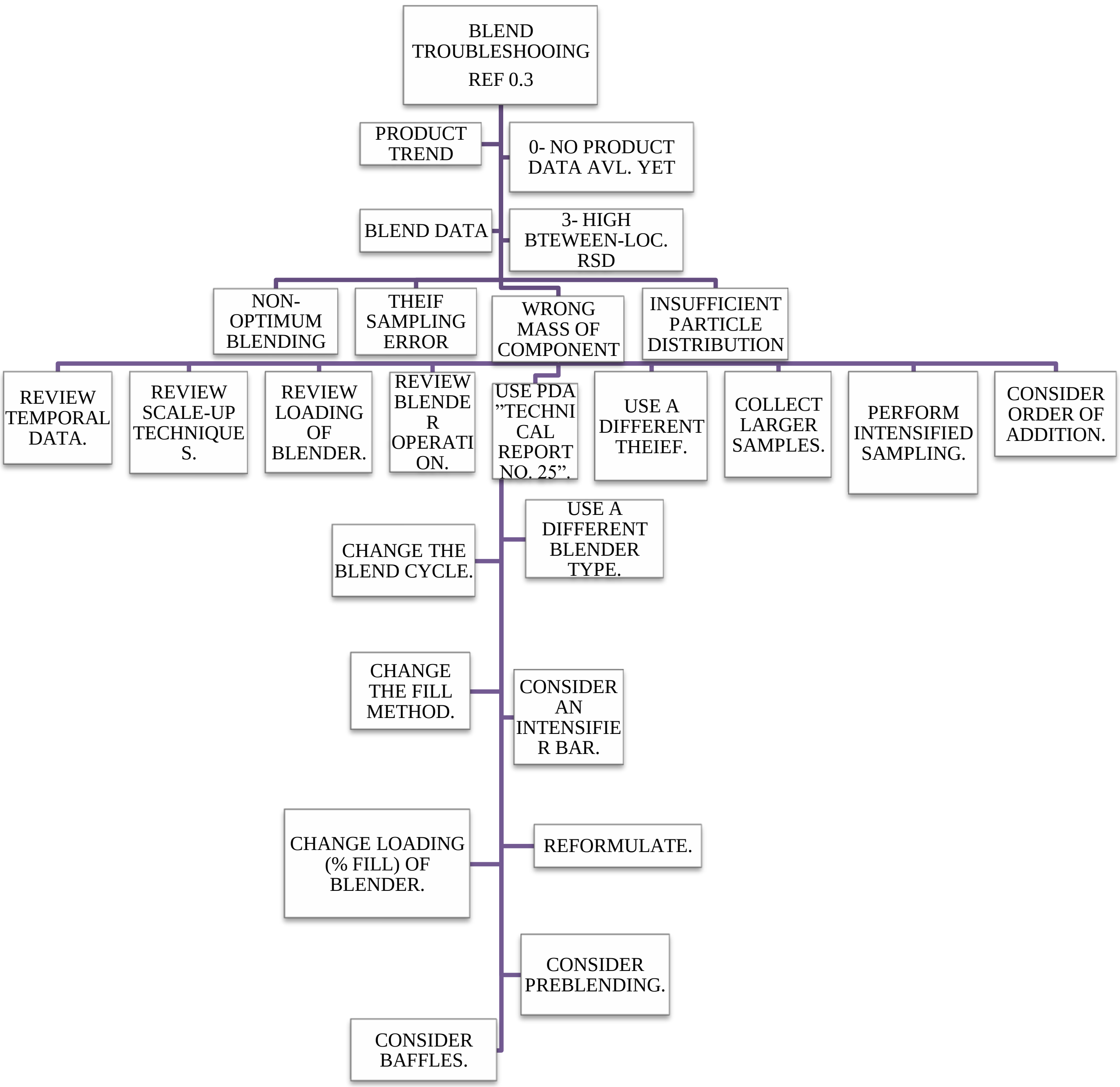


Figure 4.48: Decision tree REF. 0.4

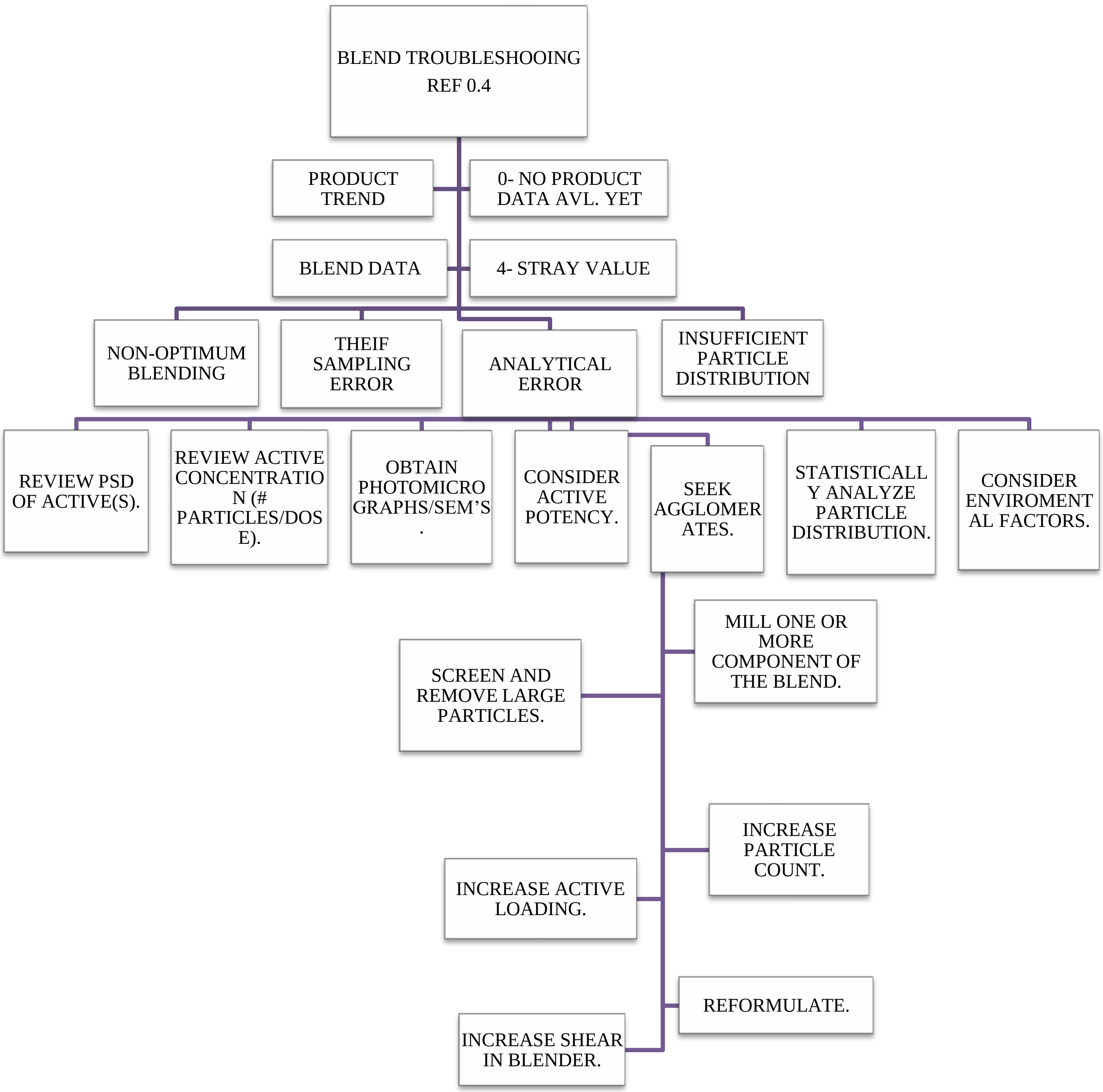


Figure 4.49: Decision tree REF. 0.5

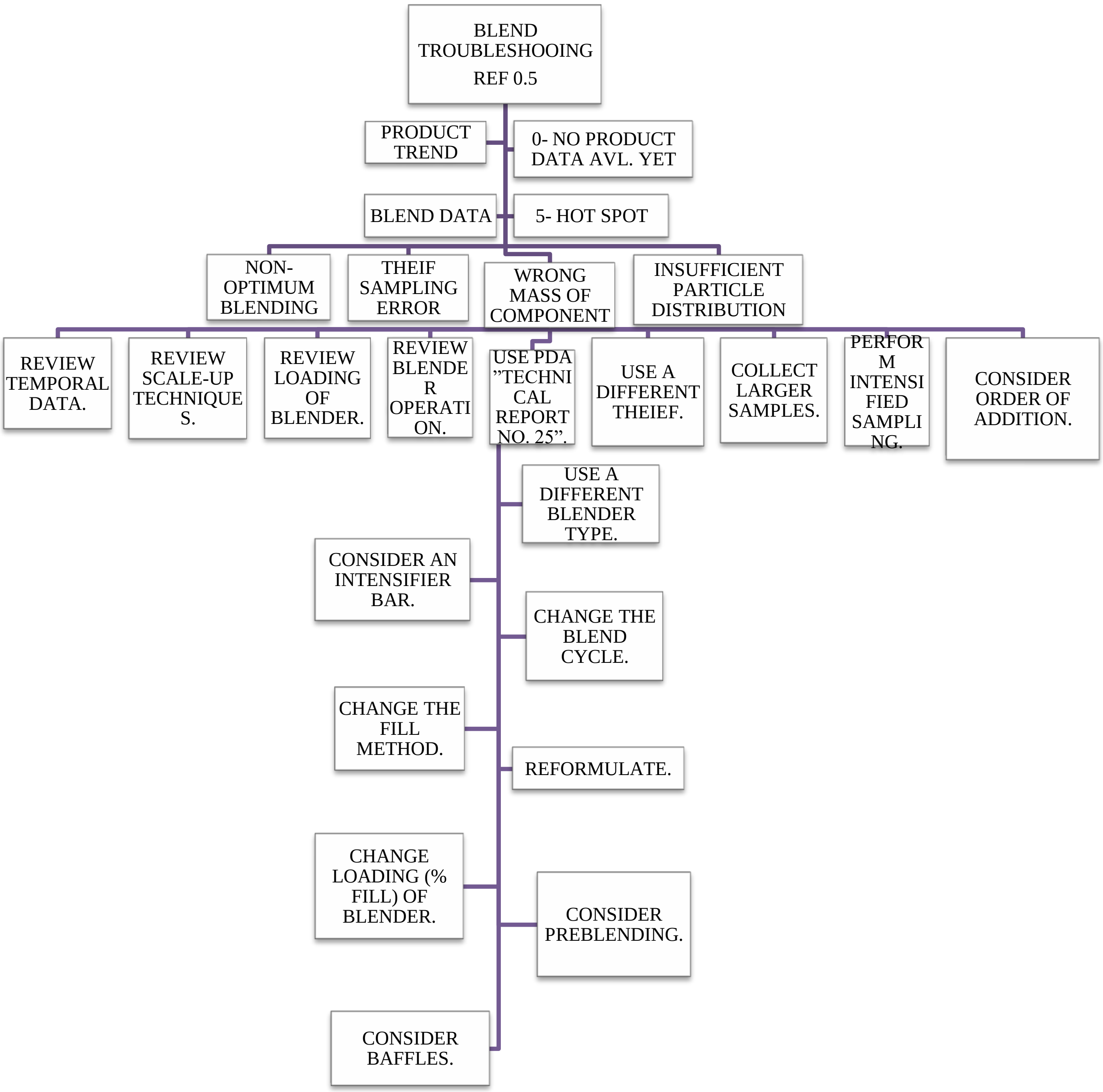
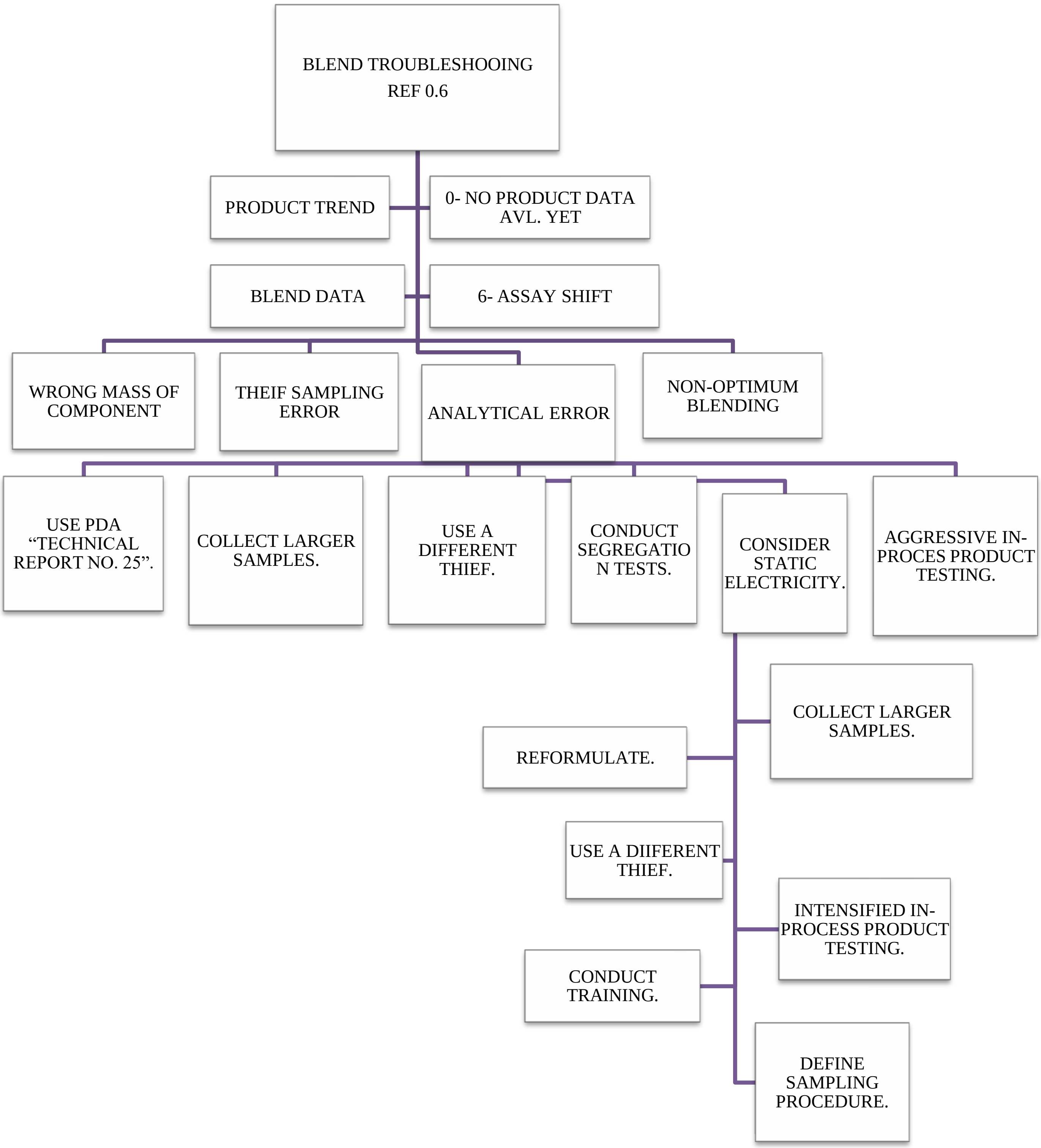


Figure 4.50: Decision tree REF. 0.6



CHAPTER FIVE

DISCUSSION

5.1 Discussion

The troubleshooting program is intended to link poor blend and/or product uniformity data to possible root causes of the problem. The program and supporting information in this thesis may be applied in principle to any powder-derived dosage form such as tablets, capsules, powder-filled bottles or vials, and sachets. The situations that are described are general behaviors only and are not correlated necessarily to any particular specifications such as the USP content uniformity test. For example, the term *high RSD* relates only to an RSD that one wishes to improve. Therefore, a failing or out-of-specification result does not need to be obtained to use this program. Many of the problematic situations presented can be improved once the root cause of the behavior is understood.

The plots in (Figures 4.1), describe the six basic trends commonly observed for product uniformity and blend samples. The data collected to prepare the plots were obtained by stratified nested sampling. *Stratified sampling* is the process of collecting blend samples deliberately from specific (planned) locations within a blender or by collecting product samples during the entire compression–filling process. *Nested sampling* is the simultaneous collection of multiple samples within a location and is required to provide the data necessary to demonstrate the variability inherent in a single location. For the purposes of this thesis, the term *sampling location* refers to a physical location in the blender (i.e., for blend data) or a sampling time during the course of the compression–filling operation. The described trends are based on tendencies of the mean, the between-location variance, and the within-location variance. Note that blend data based on samples taken outside the blender (e.g., bin or drum), though informative, are less applicable to the program because segregation may have been induced during discharge of the blender.

1. Satisfactory: Satisfactory data demonstrate that the process produces a product of acceptable content uniformity, which is reproducible for all batches see (Figure 4.1). For instances in which

the data are for the product, the product should pass Bergum's criteria; for the cases of blend data, the blend sample should comply with the standard deviation prediction interval.

2. High within-location variability: The variability of individual assay values obtained within each sampling location is wide see (Figure 4.1). When the data are subjected to component variance analysis, the within-location error term is larger than the between-location term. No clear trend of data is observed within a batch, and a consistent pattern between multiple batches is seldom observed. Potential causes of this problem include poor micro-blending, insufficient particle distribution, sampling thief error (i.e., for blend data only), or poor powder flow resulting in variable fill weights (i.e., for product data only).

3. High between-location variability: When data contain high between-location variability, although the difference in the mean values for samples taken from the various locations is large, little variability is observed in the values of individual samples within a sample location see (Figure 4.1). Component variance analysis demonstrates that the contribution of the between-location error to the overall variability observed is much greater than that attributed to the within-location term. A distinct pattern may or may not be apparent, both within a single batch and between multiple batches of product. The term *wandering* is used to describe high between-location variability for the product because the mean of the samples seems to wander over time. Potential causes of high between-location variability include poor macro-blending (i.e., quality of the blend on a large scale), segregation, and poor weight control mechanisms (for product data only).

4. Stray value: Single or multiple stray values may be observed well beyond typical variability see (Figure 4.1). The problem may not be observed in each batch because the probability of finding such samples may be low. Potential causes of stray values are agglomeration of the active, an analytical or sample handling error, or a dead spot in the blender. The magnitude and direction that the value(s) deviate from the mean can assist in identifying the problem (e.g., greater than 150–200% label claim may suggest that the sample is super potent as a result of agglomeration of the active).

5. Trending and hot spots: Trending occurs when one observes in the data a distinct direction in the assay values see (Figure 4.1). The trend maybe observed as one progresses from the top to bottom locations when sampling a blend or maybe seen as the compression filling operation progresses over time. Trending commonly is associated with product made from the end of a bin, drum, or batch and generally is repeatable from batch to batch. Although the location's mean often is substantially different from that for the remainder of the overall batch, within-location error typically is low. Potential causes of trending are segregation by particle size, which results in assay or powder density variations, or static charge bias (for blend data).

Hot spots generally are the result of incomplete blending in a specific region (i.e., a dead spot) of a blender see (Figure 4.1). Individual and mean assay values for samples taken from the hot spot are significantly greater than are those for the remainder of the batch. Unlike trends, hot spots do not necessarily occur at the top or bottom of a blender or at the beginning or end of the compression filling operation. The trouble spot generally occurs in the same location for each batch. Potential causes of hot spots are dead spots in the blender or, though less likely, biased sampling locations.

6. Assay shift: An assay shift occurs when the mean assay values are no longer centered on 100% label claim see (Figure 4.1). Both between-location and within-location errors are typically low, and the abnormality maybe repeatable between batches. Potential causes for assay shifts are the loss of one component (through adsorption or extraction during processing), analytical error, factoring or dispensing error, sampling bias (for blend data), or improper fill weight (for product data).

Potential root causes of blend or product content uniformity problems. Although, factors not discussed in this thesis could contribute to blend and product content uniformity problems, seven common root causes are as follows:

1. Non-optimum blending: Non-optimum blending results when the blender does not provide the best blend that is theoretically possible (i.e., a randomized blend of particles). Failure to achieve adequacy of mix could be the result of poor formulation development, inadequate blender

operation (e.g., fill level, loading, number of revolutions), or poor selection of blending equipment.

2. Thief sampling error: Sampling error results when the sampling device does not obtain samples that are representative of the blend. This can be caused by a number of factors such as the design and operation of the thief, the sampling technique, static charge, and the physical properties of the formulation being sampled. Sampling bias, a form of sampling error, results when there is a repeatable shift in the mean of the samples because of preferential flow of one or more components into the sampling cavity.

Note that thief sampling error can result in false negatives (i.e., the blend is poor but thief data say otherwise) in addition to the more common concern of false positives. A thief prone to false negatives is sometimes called a *counterfeiter.*

3. Segregation after discharge: Segregation occurs when the blend demixes as a result of powder transfer from the blender to the compression filling equipment. The blend also can demix in hoppers during the course of the compression filling operation. Three segregation mechanisms common with typical pharmaceutical powders are sifting, fluidization, and dusting.

Sifting segregation is a process by which smaller particles move through a matrix of larger ones. During the filling of a bin or drum, a concentration of fine particles develops under the fill point while the larger particles roll or slide to the periphery of the pile. This often results in fines discharging first, followed by coarse particles at the end of a container.

Fluidization segregation results in a top-to-bottom segregation pattern with fines at the top of a bin or drum. This can be the result of air counterflow, such as discharging from one closed container to another, or it can be caused by high discharge rates.

Dusting, or entrainment in air, results in fines accumulating at the perimeter of a bin or drum. These fines often discharge at the end of a container unless design precautions are taken.

4. Weight control: Wide variance in product fill weights can create poor dose uniformity of the finished product, even if the concentration of the blend remains uniform across the batch. Poor

weight control couldresult if the formulation possesses poor flow properties or if equipment weight controls malfunction during the compression filling operation.

5. Wrong mass or loss of component: The wrong quantity of drug substance may be added to the batch as the result of dispensing errors, improper factoring of the drug substance (for those cases in which the amount of drug added to the product is adjusted to account for inherent drug substance potency variations), or low assay values of the input drug substance. Loss of drug or excipient also can occur during processing — for example, by adsorption of a component onto an equipment surface, by becoming trapped in filter socks, or by being physically removed through powder extraction-devices.

6. Analytical error: Analytical error leads to results that are not representative of the sample collected for analysis. These errors could be the result of poor sample splitting (particularly with powder blends), dilution errors, improperly prepared standards, weighing errors, and container tare errors or vial–cap mix-ups (i.e., for blend samples).

7. Insufficient particle distribution: If the particle distribution is not considered during formulation development, the random mixture of particles can be incapable of meeting uniformity requirements. This could be the result of the particle size distribution of the drug, improper sizing of granulations, or the agglomeration of a component at any point in the process. For the particles in the system, this random variation is irreducible and not a function of blending or segregation.

The appendix discusses how a shift in assay and/or increased variability is related to root causes.

Using the solid dosage and blend uniformity troubleshooting program:

Step 1: Identify the product trend for your product. Plot the product content uniformity data as a function of sample location. Identify the product trend behavior from Figures 1–6 that is most similar to your data.

Step 2: Identify the blend sample result of your product. Plot the blend content uniformity data as a function of sample location. Again, using Figures 1– 6, identify the blend sample behavior that is most similar to your data.

Step 3: Identify a reference number. The combination of the product trends and blend sample results, in addition to those situations in which data are not available for either the product or the blend, yields 48 cases. Because the diagrams cover several tables, each of these cases is identified by a reference number for convenience.

The reference numbers consist of a composite of the product trend and blend sample result numbers. The reference number is derived in the following format: *X.Y*, where *X* is the product trend number, and *Y* is the blend sample result number separated by a period. For example, the case of trending with tablets (5) along with satisfactory blend results (1) yields a reference number of 5.1.

Once a reference number is identified, stay within that reference number's and read the table below it to identify root causes (see Step 4). Each combination of product and blend trends (i.e., the reference number) also is given a relative probability of occurring (e.g., high, medium, or low) as a result of a single root cause. If a low-probability case is encountered, multiple root causes of the problem probably are occurring.

Step 4: Identify potential root causes. This thesis identifies seven common root causes of blend sample and content uniformity problems. Each reference number has a relative probability of being caused by any of these seven root causes. For each reference number, a root cause is assigned a qualitative probability based on theoretical grounds and the practical experiences. These probabilities are presented in matrix form on the program as follows:

4 This is a common and highly likely root cause for the problem. Start your investigation here.

3 This is a likely root cause of the problem, but seek sup- porting data to confirm it.

2 There is a good chance that this root cause is contributing to the problem, but be aware of other possible causes. 1 This is not very likely to be linked to the problem, and other more likely root

causes should be ruled out first. Be aware that multiple root causes may be present. 0 It is highly unlikely that this is a contributing factor to the problem.

Seek other reasons and be aware that multiple root causes may be causing the problem. Select the highest probable root cause and start with it for the next steps. Note that in some instances several root causes have equally high probabilities of occurring. These cases warrant further investigation for multiple root causes.

As described earlier, a thief sampling error occasionally can result in false negatives. Reference numbers 2.1, 3.1, 4.1, and 5.1 all have acceptable blend data but leave open the possibility that the blend was poor even though the blend sample data looked (falsely) acceptable. For this reason, the root causes of non-optimum blending and thief sampling error are boxed together.

One should consider a number of additional points such as the entire history of the product and process when interpreting the recommendations from the troubleshooting program.

Questions one should ask include:

Is this a new product or an existing one with a significant body of data?

Has this problem been seen with this product or one similar to it?

What is unique or different about this product or process?

Have the materials, processes, operators, equipment, or environmental control changed recently?

How do the physical characteristics of the materials used for this batch compare with what was intended?

Is the problem repeatable among multiple batches, or is this an isolated incidence?

Did the operators observe any anomalies during the manufacture of the batch?

Were any equipment malfunctions encountered during batch manufacture?

How do the mean and RSD values for the blend and product compare?

How do the measured RSDs compare with the theoretical RSD of a randomized blend of particles?

**Addressing each of these questions will further help the scientist identify the cause(s) of the problem and its successful resolution.

Steps 5 and 6: Further investigations and possible solutions. Once a likely root cause has been identified, you only should click on it to Steps 5 and 6. Step 5 presents some starting points to initially consider in identifying and confirming the suggested root cause. If further investigation reveals data that do not support the root cause selected, go back to Step 4 and identify other likely root causes. Once the root cause has been confirmed, Step 6 provides suggestions for corrective actions. For example, in the case discussed above, segregation was identified as the most likely root cause.

As seen in (Figure, 5.1), this is an example about decision tree, first node is the blend troubleshooting reference number (REF. 2.3), first number (2): is the product trend content uniformity graph number, number (.3): is the blend data content uniformity graph number. Together, product trend and blend data profiles give a lead to find out the scale from (0-4), and it shown in (Figure, 5.2), by looking to the highest number it shown that there is non-optimum blending, if the problem is in the optimum blending then there is a multiple further investigation should apply to find the last solution for the problem. Through looking to (Figure, 5.1), if the problem did not finish, the final step is in the black box. But, this is a level 3 of solution and sometimes may lead to reformulate the drug.

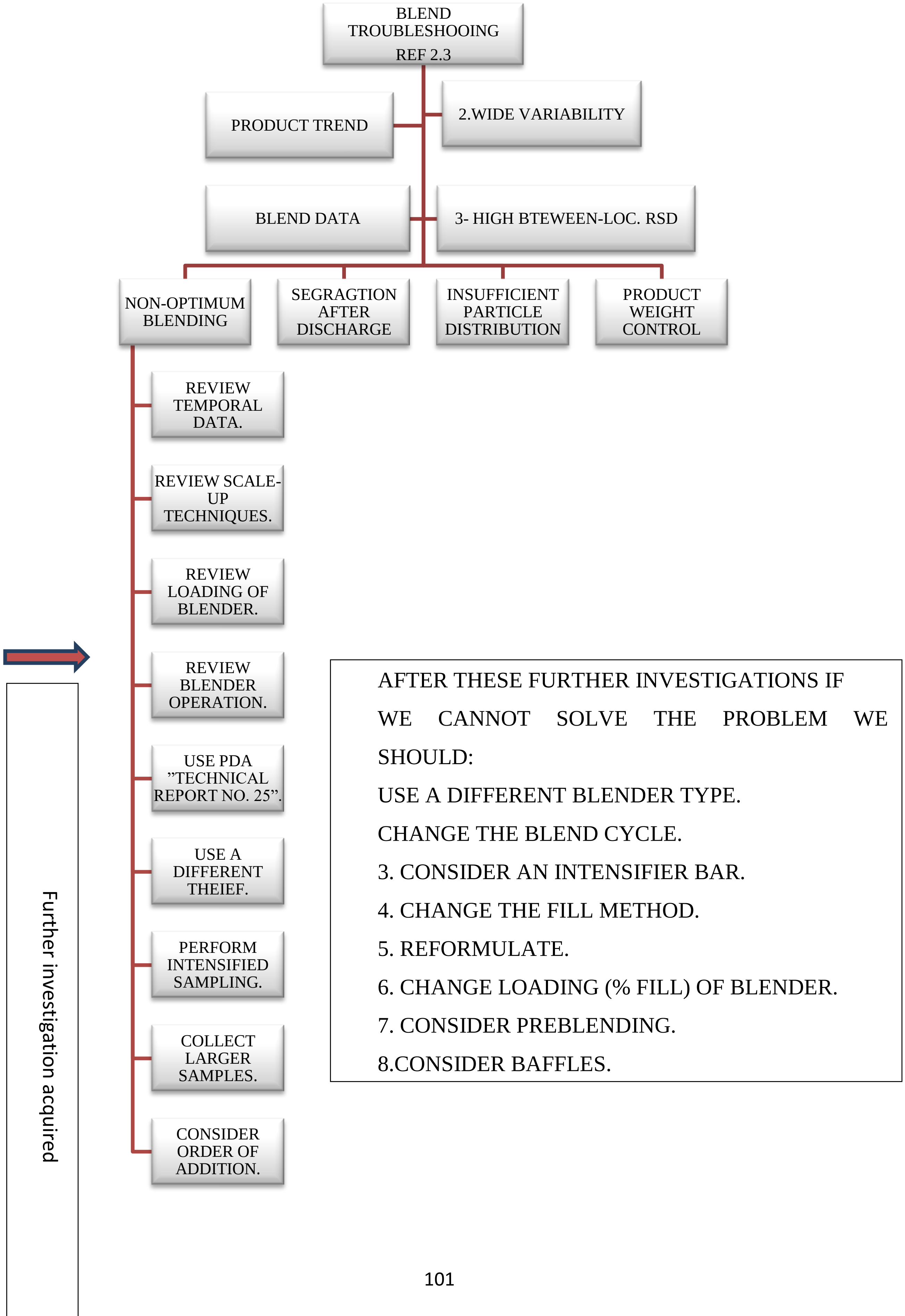
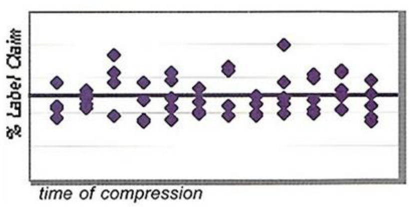

BLEND TROUBLESHOOING
REF 2.3
PRODUCT TREND
2.WIDE VARIABILITY
BLEND DATA
3- HIGH BTEWEEN-LOC. RSD
NON-OPTIMUM BLENDING
SEGRAGTION AFTER DISCHARGE
INSUFFICIENT PARTICLE DISTRIBUTION
PRODUCT WEIGHT CONTROL
REVIEW TEMPORAL DATA.
REVIEW SCALE-UP TECHNIQUES.
REVIEW LOADING OF BLENDER.
REVIEW BLENDER OPERATION.
USE PDA ”TECHNICAL REPORT NO. 25”.
USE A DIFFERENT THEIEF.
PERFORM INTENSIFIED SAMPLING.
COLLECT LARGER SAMPLES.
CONSIDER ORDER OF ADDITION.
Further investigation acquired
AFTER THESE FURTHER INVESTIGATIONS IF WE CANNOT SOLVE THE PROBLEM WE SHOULD:
USE A DIFFERENT BLENDER TYPE.
CHANGE THE BLEND CYCLE.
3. CONSIDER AN INTENSIFIER BAR.
4. CHANGE THE FILL METHOD.
5. REFORMULATE.
6. CHANGE LOADING (% FILL) OF BLENDER.
7. CONSIDER PREBLENDING.
8.CONSIDER BAFFLES.

Figure 5.1: Decision tree example.

Figure 5.2: Possible root causes table.

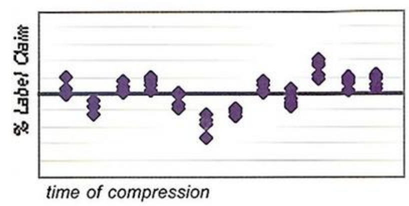
RSD OF PRODUCT				RSD OF BLEND			
WITHIN-LOC.	HIGH	BETWEEN-LOC.	LOW	WITHIN-LOC.	LOW	BETWEEN-LOC.	HIGH

PRODUCT TREND (2)



REFERANCE: 2.3

BLEND DATA (3)



POSSIBLE ROOT CAUSES	SCALE 0-4	
1-NON-OPTIMUM BLENDING	3 MACRO NON-UNIFORMITY	
2-THEIF SAMPLING ERROR	1	
3-SEGRAGTION AFTER DISCHARGE	2	
4-PRODUCT WEIGHT CONTROL	2 POOR FILL DUE TO FLOW	
5-WRONG MASS OF COMPONENT	0	
6-ANALYTICAL ERROR (PRODUCT/BLEND)	PRODUCT	BLEND
	0	0
7-INSUFFICIENT PARTICLE DISTRIBUTION	1 LARGE PS ACTIVE W/LOW DOSE	

PROBABILITY OF DETERMINING SINGLE CAUSE	MEDIUM

CHAPTER SIX

CONCLUSIONS

6.1 Conclusions

Many variables can affect a process's ability to produce a blend and product of acceptable content uniformity. In this study, anumber of potential causes leading to the content uniformity problems were discussed. However, additional factors also could be contributing to the quality of the blend and product. It should be emphasized that without proper formulation and process development, as well as the selection of appropriate blending and transfer equipment, the chances of obtaining a blend and product of acceptable uniformity are reduced significantly. The hope is that the workdescribed in this thesis will provide pharmaceutical scientists with a useful reference tool that will allow them to troubleshoot flow problems that may be encountered during the manufacture of solid dosage forms.

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