THE DESIGN OF A PILOT FACILITY FOR THE PRODUCTION OF PHEROID™ BASED PRODUCTS IN AN ACADEMIC ENVIRONMENT

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"Trials are not enemies of Faith but are opportunities to prove Gods Faithfulness"

(Anonymous)

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ABSTRACT

The initiation of this project was based on the need to produce investigational drug products for trial purposes. Such products are to be produced by a licensed GMP compliant facility. The design of the pilot facility at the NWU (Potchefstroom campus) originated from the fact that this institution had the available human resources, equipment and premises.

Feasibility investigations that had positive outcomes were conducted, with the exception of the challenge posed by the limited size of the premises and the apparent limited budget in the early stages of the project. The feasibility findings reflected that the allocated site for this project was not suitable for Pheroid production. The site was too small to contain the process requirements without increased risk to worker safety, worker comfort and materials protection. An outcome of this project was to contain the processing requirements in a defined processing vessel. The vessel thus becomes an integral and critical component of the Pheroid production process and, therefore, to the facility design.

Several investigations into process and product requirements, critical parameters, and user and regulatory requirements were done, in order to establish a conceptual model, based on the assumption that a specialised pressure vessel would be produced. As this facility design model was based purely on these requirements and on very little practical engineering knowledge, the first concept model produced was called the theoretical model (model 1).

This first theoretical design was essentially based on the process and regulatory requirements and the low budget allocated for this project. This first design required retaining, where possible, the utilities of the allocated facility in their current locations, namely the weighing area, the sink and electrical utilities, but this was not suitable in terms of process and material flow. The intent to minimise costs therefore resulted in the inclusion of an isolator unit to achieve the desired level of protection. Upon evaluation of the theoretical design by the first engineering consultant, the commissioning costs quoted to establish the isolator unit exceeded the budget requirements. The achievement of the pressure differentials to maintain the desired level of protection with the isolator area was also not practically feasible.

The cost implications of producing this first model were such that it would be very close to the cost of turning the entire facility into a fully operational cleanroom. This

scenario was vastly altered when the project received further funding that could accommodate the cost of an air handling unit (AHU), thereby achieving a higher level of protection for the entire facility. This change thus enabled the suitable location of component areas as required by material and operational flow. The impact of implementing the first theoretical design would consequently have resulted in increased lifecycle costs for the facility, as this shortcoming in the design would have necessitated correction. These alterations would have implied further costs over the facility's lifecycle, as opposed to the higher initial cost of establishment and lower maintenance cost.

Model 2 was thus designed as a cleanroom with a simple AHU so as to achieve the desired level of product protection and user requirements. It was then evaluated and it showed that the layout and capacity of the air handling system within the facilitiy was inadequate for achieving the desired level of product and material protection. A fully-fledged heating, ventilation and air conditioning (HVAC) system was then considered, in order to meet the required demands, giving rise to model 3 evolving from this set of circumstances.

Evaluation of model 3 revealed shortcomings regarding the safety requirements and the efficacy of the HVAC system. This resulted in the design of model 4 which upon evaluation met the engineering; health and safety; user's; product's; process; and material flow requirements. The model was then divided into component design requirements. Diagrammatic layouts of each of these components were established, to collectively contribute to the generation of the final architectural draft which would be used as the blueprint for the facility.

Die aanvang van hierdie projek is gebaseer op die behoefte om vir kliniese proef-doeleindes ondersoekende medisinale produkte te voort te bring. Sulke produkte sal deur 'n gelisensieerde fasiliteit wat aan GVP-vereistes voldoen, vervaardig word. Die ontwerp van die loodsfasiliteit by die NWU (Potchefstroom kampus) het ontstaan vanweë die feit dat hierdie inrigting die beskikbare menslike hulpbronne, toerusting en perseel gehad het.

Uitvoerbaarheidsondersoeke wat positiewe uitkomste gehad het, is uitgevoer, met die uitsonderling van die uitdaging wat gestel is deur die beperkte ruimte van die perseel, en die oënskynlike beperkte begroting in die vroeë stadiums van die projek. Die uitvoerbaarheidsbevindings het weerspieël dat die perseel wat aan hierdie projek toegewys is, nie geskik vir Pheroidproduksie was nie. Die perseel was te klein om sonder 'n verhoogte risiko vir werkersveiligheid, werkersgemak en materiaalbeskerming, die prosesvereistes te omvat. 'n Uitkoms van hierdie projek was om die prosesvereistes binne 'n gedefinieerde proseshouer in te sluit. Dié houer word dus 'n integrale en kritiese komponent van die Pheroid produksieproses en, derhalwe, die fasiliteit se ontwerp.

Verskeie ondersoeke na proses- en produkvereistes, kritiese parameters, en gebruiker- en regulatoriese vereistes is gedoen, ten einde 'n konsepmodel te bepaal; gebaseer op die aanname dat 'n gespesialiseerde drukhouer vervaardig sou word. Aangesien hierdie fasiliteit se ontwerp suiwer op hierdie vereistes gebaseer is, en op baie min praktiese ingenieurskennis, is die eerste konsepmodel die teoretiese model (model 1) genoem.

Hierdie eerste teoretiese ontwerp is hoofsaaklik gebaseer op die proses- en regulatoriese vereistes, en die lae begroting wat aan hierdie projek toegewys is. Hierdie eerste ontwerp het vereis dat, waar moontlik, die toebehore, naamlik die weeg-area, die wasbak en die elektriese toebehore van die toegewysde fasiliteit in hulle teenswoordige posisies sou aanbly, maar dit was nie geskik in terme van proses- en materiaalvloei nie. Die voorneme om koste te beperk het dus op die insluiting van 'n isolator-eenheid uitgeloop, om sodoende die benodigde vlak van beskerming te bereik. By evaluering deur die eerste ingenieurskonsultant van hierdie teoretiese ontwerp, het die gekwoteerde kostes om die isolatoreenheid in werking te stel die begrotingsvereistes oorskry. Bereiking van die drukdifferensiale, om met die

isolator-area die benodigde beskermingsvlak te handhaaf, was ook nie prakties uitvoerbaar nie.

Die koste-implikasies om hierdie eerste model te vervaardig was sodanig dat dit baie na aan die koste om die hele fasiliteit in 'n ten volle operasionele skoonkamer te omskep, sou wees. Hierdie toedrag van sake is grootliks verander toe die projek verdere befondsing ontvang het, wat die koste van 'n lughanteringseenheid (LHE) kon akkommodeer, wat daardeur 'n hoër vlak van veiligheid vir die hele fasiliteit bereik het. Hierdie verandering het dus die geskikte posisionering van komponent-areas, soos vereis deur material- en operasionele vloei, moontlik gemaak. Die impak van implementering van die eerste teoretiese ontwerp sou dus uitgeloop het op verhoogte lewensiklus-koste vir die fasiliteit, aangesien hierdie tekortkoming in die ontwerp regstelling sou vereis het. Hierdie veranderinge sou verdere kostes oor die fasiliteit se lewensiklus geïmpliseer het, teenoor die hoër aanvanklike koste van inwerkingstelling en laer instandhoudingskoste.

Model 2 is dus ontwerp as 'n skoonkamer met 'n eenvoudige LHE, ten einde die verlangde vlak van produkbeskerming en gebruiksvereistes te bereik. Daarna is dit geëvalueer en dit het getoon dat die uitleg en kapasiteit van die lughanteringstelsel binne die fasiliteit ontoereikend was om die verlangde vlak van produk- en materiaabeskerming the bereik. 'n Ten volle toegeruste verhittings- ventilerings- en lugversorgingstelsel is daarom oorweeg, om aan die vereiste behoeftes te voldoen, wat aanleiding gegee het tot die onstaan van model 3 vanuit hierdie omstandighede.

Evaluering van model 3 het tekortkominge ten opsigte van veiligheidsvereistes en die doeltreffendheid van die verhittings- ventilerings- en lugversorgingstelsel getoon. Dit het uitgeloop op die ontwerp van model 4, wat ná evaluering aan die vereistes van die ingenieurs, gesondheid en veiligheid, gebruikers, produk, proses- en materiaalvloei voldoen het. Die model is daarop in komponent-ontwerp vereistes ingedeel. Diagrammatiese uitleg van elk van hierdie komponente is bewerkstellig, ten einde gesamentlik by te dra tot die generering van die finale argitektuurskonsep, wat as bloudruk vir die fasiliteit gebruik sou word.

Chapter 1

PROBLEM DEFINITION AND RESEARCH AIMS

1.1 Introduction and background

The name "Pheroid™" is a derivation of the Greek term "apo-phero", which means 'to deliver'. Pheroid™ technology involves a novel drug delivery system, which is trademarked. In this dissertation the ™ symbol will be omitted, to facilitate reading. This delivery system is currently undergoing extensive testing at the North-West University (NWU) in South Africa. The Pheroid is a patented system comprising of a unique sub-micron emulsion-type formulation. "A Pheroid is a stable structure within a novel system that can be manipulated in terms of morphology, structure, size and function. The Pheroid consists mainly of plant and essential fatty acids and can entrap, transport and deliver pharmacologically active compounds and other useful molecules. Depending upon the clinical indication, it can also act in synergism with such compounds or molecules, resulting in an enhancement of the therapeutic action" (Grobler, 2004).

Whilst Pheroid-based products have demonstrated efficacy in topical delivery, research and development in this area now also concerns itself with applications of Pheroid technology in both oral and parenteral dosage forms. Bioequivalence studies, using anti-tuberculosis agents during the testing of the potential of the Pheroid-based formulation as an active transporter, has shown significant promise (Grobler, 2004).

Research involving new chemical entities intended for therapeutic purposes, as conducted by many multinational companies, differs from the research using existing drug substances within a novel drug delivery system. The Pheroid system has been shown to achieve similar therapeutic effects using lower concentrations of the known drug substances and known dosage forms (Grobler, 2004). This finding places the Pheroid system in a unique research position, i.e. one of "superavailability" of the known chemical entities in different dosage forms, thus enabling administration at lower doses. The use of lower quantities of active pharmaceutical substances to achieve the same or better therapeutic effect(s), may translate into benefits such as shorter duration of treatment and improved patient compliance.

The Pheroid drug delivery technology, discovered in South Africa and now owned by the North-West University (NWU), has advanced to the early stages of clinical trial

testing. The NWU is currently developing an investigational product for clinical trial purposes. This product would not only have to meet the production process requirements regarding quality, but will also have to be manufactured according to good manufacturing practice (GMP). Currently, Pheroid-based formulations are made in experimental laboratories at NWU and the scale of the equipment available does not allow for production of more than 10 kg of bulk product at a time. The in-process and final product testing of the experimental batches are also done at NWU.

The production of pilot scale batches was initially due to be out-sourced to the pharmaceutical industry. However, upon investigating that option, it was found that none of the eligible sites had the necessary equipment (or the willingness to invest in it). This problem also extended to in-process and final product testing. The pilot plant previously utilised for manufacturing of the pilot batches at MeyerZall Laboratories (George, Western Cape), was closed down. Any other facility could, if necessary, improvise production equipment to suit the Pheroid production process but still present with difficulties in terms of the necessary in-process control tests and final product release, since the measurement of the zeta potential and confocal laser scanning microscopy (CLSM) confirmation of Pheroid formation are critical. None of the equipment necessary for analytical testing was available at this facility. This also implied having to send these samples back to NWU for analysis.

Two other manufacturing sites (Alliance and Divpharm) may become compliant for contract manufacturing of Pheroid-based products provided that these contract manufacturers are willing to modify and / or upgrade existing equipment. The equipment to be used for production includes, amongst others, a specialised pressure vessel (unique to Pheroid production) which would be able to accommodate the long gassing periods of ingredients whilst maintaining a pressure of 200 kPa. The contract manufacturers envisage a relatively large investment in equipment that would only be used to produce pilot-scale investigational product and thus anticipate poor returns on the overall life-cycle cost of the equipment.

Whilst it may be possible to obtain the equipment (with financing in place), in most cases, the process would involve sampling and sending these samples to NWU for testing, in order to verify Pheroid formation. Entrapment of active ingredient occurs during or after Pheroid formation and the entrapment efficiency of the active ingredient also has to be determined. The in-process control tests to ensure that Pheroid formation has taken place, includes zeta potentiometry, CLSM and particle size analysis. The equipment required for CLSM observations and zeta potentiometry are

not found in analytical laboratories as a matter of course – there are only two confocal laser scanning microscopes in South Africa, one of which is located at NWU. The transportation of these samples for analysis is expensive, especially when samples of both before and after entrapment have to be sent for analysis. Transportation of these samples also subjects them to agitation that substantially affects the degree of degassing that takes place before entrapment. This in turn, affects the stability of the Pheroid formed (Uys, 2006).

1.2 Motivation for design of a pilot plant

1.2.1 Investigational drug product

There has been a significant move on the part of regulators to harmonise the rules and regulations regarding medicinal products. Global players in primary health care regulation such as the Federal Drug Administration (FDA), Medicines Control Agency (MCA), Japan Pharmaceutical Manufacturers Association (JPMA) and World Health Organisation (WHO) are co-operating to rationalise rules, to reduce risks and to improve safety profiles with respect to the manufacture of medicinal products. The South African Medicines Regulatory Authority (SAMRA) has shown a similar trend, particularly after recently being granted membership of the Pharmaceutical Inspection Co-operation Scheme (PIC/S).

In the past, most of the manufacturing industry gave minimal attention to process, personnel and waste flow patterns. Whilst efficiency was sought after in meeting production demands, little emphasis was given to GMP compliance. The pharmaceutical industry is dynamic and its progress leads to the evolution of regulatory demands. The regulatory requirements for investigational drug products used in clinical trials are that such products must be produced in accordance with good manufacturing practice (ICH, 1996). It is therefore important that production of this investigational drug product be carried out by a licensed manufacturer able to comply with the process requirements of this novel drug delivery system, without risk of:

i. compromising quality and / or stability;

ii. incurring huge costs due to lack of production and / or analytical equipment; and

iii. delays due to inadequate facilities and limited budgets.

1.2.2 An alternative approach

An alternative to subcontracting would be to manufacture the investigational product at an academic institution like NWU. However, at the outset, such a facility would have to be designed to be GMP compliant. To date, the GMP requirements are that the various operations and processes be performed in specifically defined areas. Facilities have to be designed in a manner that allows for acceptable flow patterns of material, personnel and product. Cognisance must be taken of the fact that the manufacturing requirements for the modern pharmaceutical industry are increasingly complex and with much emphasis on the concept of quality by design. Signore (2005), in the approach to GMP design, indicates that the pharmaceutical industry profile is increasingly subject to imperatives of cost, value, safety and complexity and that these are respondent to the strategic manufacturing drivers within an evolving compliance framework.

When the alternative approach of manufacturing this delivery system at an academic institution was considered, the benefits of establishing a pilot facility were weighed against the likely challenges that would be encountered. The benefits and challenges identified were:

1.2.2.1 Benefits of the alternative approach

i. The testing for Pheroid formation would be more cost effective and less time consuming.

ii. The efficiency of drug entrapment could be determined within a matter of hours.

iii. A custom-designed facility could be built, to reduce risk of contamination and to optimise the production process, thereby minimising transfer times.

iv. Greater control over the manipulation of physical characteristics such as particle size and morphology would be possible.

v. The Pheroid production facility (premises and equipment) could be designed to follow the principles of *quality by design*.

vi. The confidentiality and classified nature of the various Pheroid-based research projects would be better protected at a research facility of such an academic institution.

vii. Existing expertise in Pheroid production would be immediately available and at hand.

viii. Viable, marketable products could be developed in a shorter period of time.

1.2.2.2 Anticipated challenges of the alternative approach

The challenges anticipated for the production of investigational products at this academic institution (NWU) would include:

i. Dedicated space would have to be allocated for the establishment of a plant.

ii. The plant design would have to meet both process and GMP requirements.

iii. Team members would have to invest a large amount of time to design and develop the desired facility, despite research in this field still only being in its development phase.

iv. Funding would have to be obtained to finance the plant.

v. Upscaling of this process may present with unforeseen challenges.

1.2.2.3 Selection of the alternative approach

Pheroid production is an entirely new endeavour in pharmaceutical science. In terms of regulatory and academic institutional norms and values, establishing a pilot facility at an academic institution is in its infancy. At the time of going to press, as far as it is known, there appears to be only one academic pilot facility that has been licensed by SAMRA (SADOH, 2007). Nevertheless, in recent years a trend has been observed in the United States whereby academic institutions have engaged in developing GMP facilities that are not research laboratories, but are facilities capable of manufacturing pharmaceutical products for early phases of clinical research (Perciali, 2007). While this development is apparent in the United States, it is a fairly unfamiliar concept in South Africa.

Although various challenges in manufacturing Pheroid at an academic institution exist, they are far outweighed by the benefits of establishing such a pilot plant for the production of Pheroid-based products in the academic environment.

1.3 Research aims

The scope of this study is to investigate and propose a design for a GMP compliant pilot facility that is located within an academic environment, namely the North-West University.

The design proposed should

i. meet the Pheroid production process requirements;

ii. comply with current Good Manufacturing Practice (cGMP);

iii. produce investigational products suitable for the purpose of conducting clinical trials both in South Africa and internationally.

1.4 Study Outline

Identification of the problem and the aims of this study (Chapter 1) is followed by a literature study on Pheroid technology within the context of nano- and micro-particulate delivery systems in Chapter 2. Chapter 3 contains a literature review, which explores the regulatory and production frameworks of pilot facility design for investigational drug products. Chapter 4 includes discussions of the findings of the empirical investigations, the presentation of a proposed theoretical design and the results of the practical evaluation of the theoretical design. It includes three phases of the re-working of the model, in order to propose a draft for the final architectural design. Chapter 5 provides the final architectural design of the pilot facility, the recommendations and conclusion of this study. Annexure A contains the empirical investigation findings of the study. An A3 size of the architectural draft of the final design is presented in Annexure B. An article format of this study, described according to section A.13.7.3 of the general academic rules of the North-West University, is presented in Annexure C. This article is presented in accordance with the prescribed author guidelines for publication in the South African Pharmaceutical Journal (SAPJ).

Chapter 2

NANOTECHNOLOGY, MICROSPHERES AND PHEROID

2.1 Introduction to nanotechnology

Pheroids are nanoparticles consisting mainly of essential fatty acids. Nanotechnology encompasses particle-engineering technology in which drug delivery, through increased efficacy and / or safety, improves patient compliance. The process of forming nanoparticles was designed with the intent of producing required particle characteristics of a medicine for enhancing the performance of the product (Hu *et al.*, 2004).

Recently, four particle-engineering technologies that specifically aim at reducing drug particle size in order to enhance wetting, dissolution rate and bioavailability of drugs that exhibit dissolution-rate limited absorption, have been reported. These processes are known as evaporative precipitation into aqueous solution (EPAS), controlled precipitation (CP), spray-freezing into liquid (SFL) and ultra rapid freezing (URF) (Hu *et al.*, 2004).

The EPAS technology utilises rapid phase separation by which to produce an aqueous dispersion of stabilised drug nanoparticles. This process involves the use of a volatile organic solvent. When the solvent evaporates, it supersaturates the aqueous phase with the active ingredient, causing rapid precipitation in the form of suspended particles.

During the CP process the hydrophobic drug is dissolved in a water miscible organic solvent that is rapidly and controllably mixed with an aqueous phase, causing sudden supersaturation of the drug in the aqueous phase. This leads to rapid nucleation and the formation of small particles.

SFL is a cryogenic process that uses processes of atomised spraying and rapid freezing to produce primary drug nanoparticles. URF also utilises rapid freezing of the feed solutions of drug excipients, to produce micron to sub-micron aggregates of amorphous nanoparticles (Yu *et al.*, 2006, Vaughn *et al.*, 2005 & Hu *et al.*, 2004).

2.2 Micro-encapsulation

Micro-encapsulation of solids or liquids by polymer coating and entrapment into polymer matrices results in a colloidal carrier system. This is often used in

pharmaceutics to improve the stability of drugs to modify or delay drug release. This process is essentially based on solvent evaporation methods and phase separation. In general, the micro-encapsulation technique comprises of an oil / water emulsion system enabling the drug to be dispersed or emulsified in an organic polymer solution. This system is then emulsified in an external aqueous or oil phase (Rè & Biscans, 1999).

2.3 Microsphere formation by emulsion-solvent diffusion method

In the emulsion-solvent diffusion method of microsphere formation the physical state of the dispersed phase is coupled with mass transfer (solvent diffusion) to determine the progression of microsphere formation. Rè & Biscans (1999) classify the stages observed in the physical state of the polymer solution as follows:

i. Solution state;

ii. Gel state and

iii. Glassy state.

This process, described by Rè & Biscans (1999) for a water insoluble drug, entails the admixing of a polymeric solution containing the dissolved drug in an organic solvent (such as acetone) dispersed into an aqueous phase. An oil / water emulsion is formed whereby the solvent rapidly diffuses out of the emulsion droplets into the aqueous medium.

The instantaneous mixing of the solvent and water at the interface of the emulsion droplets induces precipitation of the polymer forming a film-like membrane enclosing the solvent and the dissolved drug, which is still in the solution state.

With the progression of the solvent and water counter-diffusion processes, the polymeric solution in the emulsion droplet becomes more concentrated leading to a solution gel transition.

Further solvent and water counter-diffusion through this film-like membrane promotes drug crystallisation. This induces glass transition on the polymeric film at the periphery of the droplets. When this process has run its course, the microspheres are in a glassy state and the solidification of the polymeric membrane is complete.

The different stages in the physical state resulted in different drug release rates. The process of solidification and water uptake are factors that compromise microsphere formation (Rè & Biscans, 1999).

2.4 Pheroid

Pheroid technology, previously called Emzaloid™ technology, is a patented drug delivery system. Pheroid technology presents the following key advantages:

i. Enhanced delivery of active drug substances;

ii. Reduced time to onset of action;

iii. Reduction of minimal effective concentration;

iv. Increased therapeutic efficacy;

v. Reduction in cytotoxicity;

vi. Penetration of most known barriers in the body and in its cells;

vii. The ability to target treatment areas;

viii. The lack of immunological response;

ix. The ability to transfer genes to cell nuclei; and

x. The reduction of drug resistance (Grobler, 2004).

Whilst there are many existing delivery system technologies such as lipid-based carriers or viral vectors, the Pheroid is unique among these, in that its components are manipulated in a very specific manner to ensure its high entrapment capabilities, very fast rate of transport, delivery and stability. The absorption capabilities and drug release characteristics of the Pheroid can thus be controlled. The entrapment of actives within the Pheroid creates a more effective formulation than one involving the said active alone (Grobler *et al.*, 2008).

2.4.1 Types of Pheroid

The formulation of Pheroid types can be varied by manipulation of composition and manufacturing method (Grobler, 2004), for example:

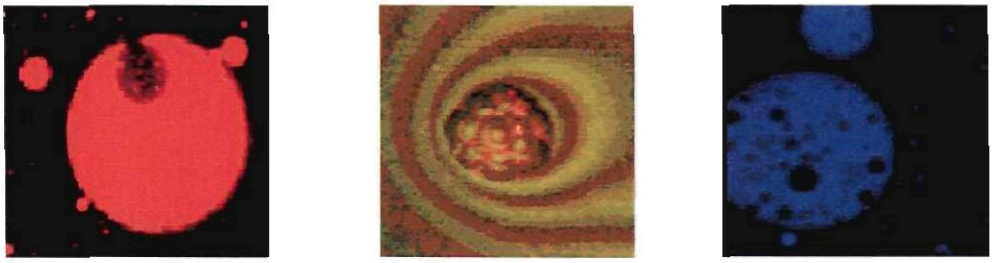
i. Lipid-bilayer vesicles in both the nano- and micrometer size range;

ii. Pheroid microsponges; and

iii. Pro-Pheroid that is contained in depots or reservoirs (Grobler, 2004).

The composition of each of the above-mentioned systems is specific. The size and shape of these vesicles can be reproducibly controlled (typically between 0.5 - 1.5 µm), while that of the Pheroid micro-sponges usually range between 1.5 – 5 µm. The sizes of depots or reservoirs are determined by the amount of pro-Pheroid contained in these reservoirs (Schlebusch, 2002). As with liposomes, Pheroids generally contain a lipid bi-layer, but contains no phospholipids or cholesterol, whereas Pheroid microsponges and depots support prolonged release in accordance to a concentration gradient (Grobler, 2004).

Figure 2.1 shows confocal laser scanning micrographs (CLSM) of various formulations of the Pheroid delivery systems (Grobler, 2004).



(a) (b) (c)

Figure 2.1 CLSM pictures of Pheroid, pro-Pheroid and Microsponges, Figure 2.1(b) was adapted from "Background to Emzaloid" (Grobler; 2004).
(a) A Pheroid depot with Pheroid vesicles in the background.
(b) The formation of small Pheroids from a pro-Pheroid formulation.
(c) Microsponges - the reservoir contains multiple particles. Reservoirs have large loading capacities to surface area and are good entrappers of insoluble compounds.

In contrast with liposomes, Pheroids are formed by a self-assembly process similar to that of low-energy emulsions and micro-emulsions, and no lyophilisation or hydration of the lipid components are necessary. Grobler *et al.* (2008) states that Pheroids are dispersed within a dispersion medium, as in emulsions, and contain not only two liquid phases but also a dispersed gas phase which is associated with the fatty acid phase. Therefore, the Pheroid system differs substantially from conventional macromolecular carriers such as liposomal delivery systems (Grobler *et al.*, 2008). Grobler (2004) has

tabulated the similarities and differences between a typical lipid-based delivery system and that of the Pheroid delivery system. Amongst the differences listed are:

i. fatty acids in Pheroid have an affinity for cell membranes that enhances the penetration and, therefore, the delivery of entrapped drugs;

ii. Pheroid has capabilities of entrapping drugs of different solubilities, including water insoluble drugs;

iii. a possible mechanism of intracellular release of drug occurring beyond the membrane zone that is found in drug resistant organisms;

iv. Pheroid entrapment of drugs reduces the volume of distribution and increases target concentrations (Grobler, 2004).

2.4.1.1 The pro-Pheroid concept

The Pheroid dispersion system consists of the interspersion of two liquid phases and a gas phase. The two liquid phases consist of an aqueous base and an oily base (Grobler *et al.*, 2008). Pro-Pheroid formation thus involves the process of gassing the oily phase with nitrous oxide, followed by mixing the drug into this oily phase. The pro-Pheroid thus consists of an oily-base liquid phase that is interspersed with the gas phase, and is almost a 'pre-cursor' for the formation of Pheroid. On introducing the aqueous liquid base to the oil phase, Pheroid formation takes place. With oral ingestion of a drug dispersed in pro-Pheroid, Pheroid formation would take place in the stomach. These pro-Pheroid systems are produced in the absence of the aqueous phase and have a larger polyethylene glycol content than that of Pheroid formulations, in order to facilitate increased bioavailability, increased stability and enhanced drug solubility (Grobler, 2004).

2.4.1.2 Pheroid microsponges

In their study on novel carrier systems, Vyas & Khar (2002) have defined microsponges as porous microspheres having a myriad of interconnected voids ranging in size from 5 to 300 µm. These microsponges have the capacity to entrap a wide range of active ingredients such as emollients, essential oils, anti-infective agents, etc. Pheroid microsponges are 1.5 to 5 µm in size, with cavities in the nano-size range, i.e. much smaller than those described by Vyas & Khar (2002).

The size, stability, absorption characteristics and entrapment capabilities of the Pheroid microsponge can be manipulated by changes in temperature, agitation / sheer and variation of fatty acids in the formulation (Grobler, 2004).

2.4.2 Pheroid formation

Grobler *et al.* (2004) state that "Pheroids are formulated primarily of ethylated and pegylated poly-unsaturated fatty acids, including the omega-3 and omega-6 fatty acids but excluding arachidonic acid. The specific ratio of the pegylated to ethylated fatty acids used in the assembling of the Pheroids adds some of the reservoir characteristics of the polymeric microspheres, whilst the formulation of natural depots is reminiscent of the structure of macromolecular microspheres".

Pheroid formation is dependant on the presence of nitrous oxide (N_2O). The N_2O increases the miscibility of the fatty acids with the dispersal medium and contributes to the stability of the formed Pheroids. Thus a critical process requirement in Pheroid production is gassing with N_2O (Uys, 2006).

2.5 Conclusion

It is noteworthy that the Pheroid does indeed meet the criteria for classification as a nanoparticle. However, it does not fit in with the four particle engineering technologies as defined by Hu *et al.* (2004).

The Pheroid is a nanosphere formed through a mechanism that falls outside of the four-particle nanotechnology. The formation of the Pheroid is largely based on gassing with nitrous oxide (N_2O). Molecular modelling suggests that stable Pheroid vesicular structures are formed due to the interaction between the fatty acids and nitrous oxide. The nitrous oxide essential fatty acid (NOEFA) matrix forms the basis from which the Pheroid can be effectively used as a novel drug delivery system, by which to transport both hydrophobic and hydrophilic drug substances (Grobler *et al.*, 2008).

This Pheroid-based product can also be termed "*a colloidal system occurring as the result of micro-encapsulation*", as described by Rè & Biscans (1999). However, it does not follow the mechanism of micro-encapsulation, as solvent evaporation and resultant drug precipitation is not the mechanism followed in Pheroid formation. Pheroid formation occurs in the absence of drugs and solvents. However, the entrapment of a drug by the Pheroid may occur after the process of Pheroid formation.

The Pheroid formation can also be said to have similar characteristics as microsphere formation, as described by Rè & Biscans (1999), but it fails to move beyond the solution phase into either a gel or glass state.

Chapter 3

FACILITY DESIGN AND REGULATORY REQUIREMENTS

3.1 Introduction

The general perception and role of a pilot facility centres on the understanding that it may serve as the bridge between the experimental / developmental studies and full-scale manufacturing. The pilot facility described in this study would have to be adapted, to provide for the facility to be:

i. based at an academic institution, namely the North-West University, South Africa;

ii. dedicated to the production of Pheroid-based products (PBP);

iii. used for the production of investigational (clinical trial) drugs that are PBP;

iv. in line with the regulatory requirements and current GMP (cGMP) practices.

Initially, an attempt was made to identify factors that are relevant to the pilot facility design by scrutinising available literature. This included a search for the characteristics of manufacturing facilities based at academic institutions, regulatory requirements for pharmaceutical production facilities and characteristics of Pheroid and Pheroid production. These three aspects were used to guide the design of a pilot facility located within an academic environment.

3.2 Pilot facility design

3.2.1 Distinction between experimental facility and pilot facility

The challenge encountered, both during and after product development, is the production of investigational product batches for clinical trials, while maintaining vigilance in respect of the need for developmental changes and the up-scaling, later, to production volumes. Tovey & Baker (1999), in their review of shaping the modern pharmaceutical development facility, describe these as divergent activities. They state that the pilot facility requires full cGMP (discussed in paragraph 3.2.3) while the focus of the other is on experimentation and development only. They further elaborate that mixing the activities of these two types of facilities and attempting to maintain full cGMP simultaneously, is difficult and that some companies avoid this issue by providing separate facilities (Tovey & Baker, 1999).

Batches produced for clinical trials and pilot batch studies for stability determination both have to be manufactured according to cGMP standards and require careful documentation (SADOH, 2005). On the other hand, formulation development and resolution of technical / developmental problems remain focused on solving problem(s) rather than providing material made to a specific standard. It is therefore clear that a pilot plant and a development facility would have different standards. Allowing 'dual standards' of meeting regulatory requirements in some aspects and researching without implementing regulatory requirements to co-exist within the same facility has obvious limitations.

3.2.2 Commercial versus academic pilot facility

Pilot facilities are scarce, since many Research and Development installations are sponsored by pharmaceutical industries, who are themselves championing the development of new drug products. These industries generally make use of their own associated pharmaceutical production facilities to generate their pilot batches.

Commercial and academic production facilities are governed by the same national regulations, but have different resources, business practices and goals. Compared to industry, both in terms of facilities and personnel, most academic institutions have very limited resources for use in manufacturing. Academic institutions are also often involved with new technologies that may still be in preliminary stages of research and development. In addition, academic institutions often undertake so-called orphan projects, of which the applications are too limited to be economically viable for corporate development (Steel & Roessler, 1999).

Given the circumstances above, the purpose and / or function of the pilot facility would thus include the production of test material or product(s) for clinical trials and pilot batch studies (stability determination). These functions do not require full size production batches. It is usually also not financially prudent to use full production-scale batches for testing purposes.

Thus, in order to determine the acceptable scale and criteria to be used in defining the 'pilot batch size', the following must be considered: The scale of manufacture of a test batch should be equal to a minimum of the pilot scale or larger; using a manufacturing process that meaningfully simulates what would be used in the large-scale production. As a rule of thumb, 10% of the production scale is often used for solid dosage form manufacture (WHO, 1997), where a minimum for full scale batch sizes for oral solid dosage forms (OSD) would be 100 000 tablets or capsules, and 100 kg minimum for

oral liquid dosage forms (OLD) (SADOH, 2005).

In the pharmaceutical industry, the role played by pilot facilities is becoming obsolete. In the academic situation, however, the need to have a facility in which to produce the prescribed batch size in a manner that meaningfully simulates the potential full batch size, while still complying with GMP requirements, is becoming indispensable.

The role of pilot facilities is not only critical in establishing drug manufacturing processes and for performing process validation, but also for setting the standards for good manufacturing practice (Bequette *et al.*, 2004). As prescribed by the South African Medicines Regulatory Authority (SAMRA), any pharmaceutical manufacturing facility is obliged to comply with these GMP guidelines.

It is evident, therefore, that the manufacturing tasks and processes conducted in this facility, have to be validated against the standards set for GMP compliance in that facility.

3.2.3 Approach to Good Manufacturing Practice design

Good Manufacturing Practice (GMP) sets parameters within any system, for ensuring that products are consistently produced and controlled in accordance with quality standards. These parameters are designed to minimise those production risks that cannot be eliminated through testing of the final product (WHO, 1992).

The principles of GMP applies to all aspects of production; ranging from the starting materials, premises and equipment to the training and personal hygiene of staff. The WHO advocates that detailed written procedures are necessary for any process that impacts on the quality of the final product. GMP must thus include the provision of systems by which to provide documented proof that correct procedures are consistently followed at each step in the manufacturing process every time a product is made (WHO, 2003). As the pilot facility intended for manufacture of Pheroid products is based in South Africa, it is essential to identify the facility GMP requisites as per the South African guidelines.

While it can be assumed that regulations require a disciplined approach to the design of pharmaceutical manufacturing facilities, such an approach is not prescribed by the regulators. Various contributors to the International Society of Pharmaceutical Engineering (ISPE) baseline guides have indicated that the approach to GMP is rather to ensure good design practices that form the foundation for the design of a suitable manufacturing facility.

According to Del Ciello (2005), the foundation of good design practice (GDP) is to take into consideration the manufacturing process(es) and the product(s) that would be produced, tested, or held in the facility under design. Del Ciello (2005) advocates further that the majority of design decisions and design criteria should be based on the critical quality attributes of the product, and the designer should therefore have knowledge of how the facility is to operate and how it is to be validated.

The manufacturing process and facility requirements are defined and refined during the development stage(s) of the design. These requirements also need to be developed through discussion with the end user(s), which includes those individuals involved with the manufacturing, quality assurance (QA) / quality control (QC), as well as the engineering, validation and construction groups (Del Ciello, 2005).

Four basic stages or phases in the approach to GMP design has been outlined by Del Ciello (2005), i.e.:

a) establishing the objectives of the facility;

b) understanding the process requirements and setting the specifications based on criteria established in terms of process;

c) establishing the operational flow; and

d) developing a facility conceptual design.

The first phase in GMP design encompasses the objectives and goals, and embraces the corporate philosophies, operating philosophies and regulatory requirements of the intended design. The operating philosophy encompasses the policies and / or decisions regarding the presence or absence of process material quarantine areas, etc. during manufacturing operation and which, in turn, will affect the operational size and layout of the facility.

GMP regulations place restrictions on the design of a facility, and question, for example: 'How are material controls to be ensured during production?'. An understanding of these factors is thus essential in designing a GMP-compliant manufacturing facility.

The second stage concerns the user requirement specifications, process flow and operations. At this stage, the designer understands that the objective is to deliver a

design for a facility that must be licensed and does not just entail the designing of a building filled with equipment (Del Ciello, 2005).

The manner in which the facility, equipment and systems will be utilised, forms the foundation of the manufacturing operation. The arrangement of various production elements in the facility flows from, and depicts, the connection between the different manufacturing process steps, such as QA, production, in-process testing, etc. It is therefore quite possible for the designer to incorporate the entire operation into the layout of the facility without inadvertently neglecting some component or preventing required interactions.

The third stage that was identified, addresses the 'system design criteria'. Since the manufacturing requirements of the desired products form the focus for establishing the design criteria, it is necessary for an analysis of the manufacturing process to be conducted, in order to understand these process requirements and the process flow. This knowledge and insight will ensure that the necessary support systems required to facilitate the process would be considered, as these factors could seriously impact on the quality of the product and the efficiency of operations.

The final stage involves the 'facility conceptual design'. The conceptual design of the facility develops as the manufacturing process flow diagram is established. The concepts for the support utilities such as water supply are derived when the quantity / extent of use of the specific utility is known then decisions regarding the segregation of process and building utilities can be made. Once the manufacturing process and support utility requirements are identified / set out, the facility layout can be developed.

At this stage the engineering and validation disciplines are engaged, with the aim of developing an approach to validation and commissioning. A report delineating the facility requirements and presenting the concepts involved, including the sketches and a schematic architectural design of the facility, should then be generated. This report forms the basis of what the facility design and development outcome will be. At this stage a meeting with the regulators should be convened, to conduct a GMP audit of the project. The purpose of this audit would be to determine whether the design of the facility meets cGMP design or not.

Any re-working of the design would thus also be based on the audit feedback from the regulators (Del Ciello, 2005). Unfortunately, the service of GMP auditing a facility

design / plan, as carried out by the FDA, has not been the practice of the South African regulatory body, according to Mr. E. Mochitela (2006).

The South African GMP guidelines, as it applies to pharmaceutical manufacturers, contain several critical considerations that are useful in ensuring that the necessary issues of quality in production facilities are adequately addressed. Amongst others, these include: quality management, personnel, premises and equipment, documentation and production.

3.2.3.1 Quality management

Licensed manufacturers in South Africa are obliged to manufacture medicinal products in such a manner that these medicines are fit for their intended use and comply with the requirements of medicine registration. This ensures that users / patients are not placed at risk due to poor quality, safety and / or efficacy. To achieve this, a comprehensive, well designed and correctly implemented system of quality assurance, incorporating good manufacturing practice and quality control, is required. GMP forms part of this quality assurance, which enables a product to be consistently produced and controlled to the quality standards appropriate to its intended use, and as required by the medicine registration or product specification (SADOH, 2005).

The supplementary GMP training guide of the WHO has identified the following factors that contribute to the quality, or lack thereof, of the final product:

i. Starting materials and packaging materials;

ii. Validated processes;

iii. Personnel;

iv. Procedures;

v. Equipment;

vi. Design and quality of premises;

vii. Manufacturing environment.

These factors are all inter-related as reflected in figure 3.1.

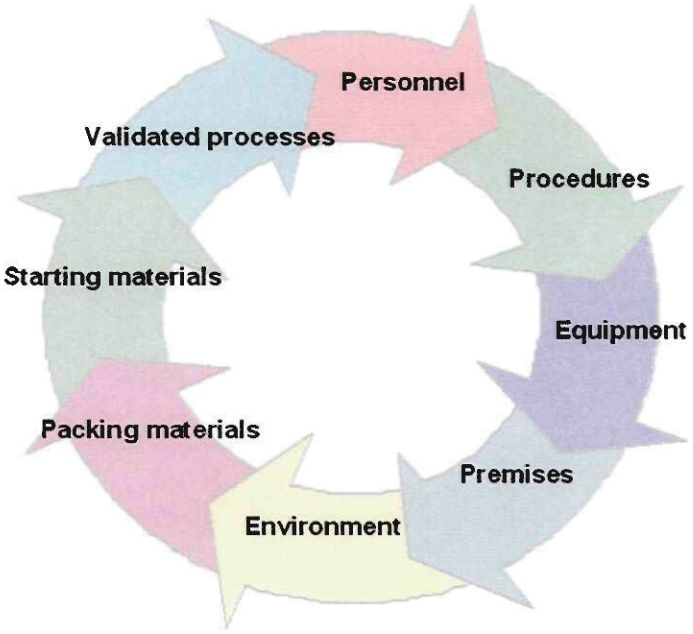


Figure 3.1 Factors contributing to quality product (adapted from WHO, 2006).

Inadequacies in any of these factors could ultimately lead to sub-standard products. The SADOH (2005) GMP guide essentially quotes the same requirements. Therefore, the section of guideline 1.3.2, that is deemed relevant to facility design intended for medicine manufacture in South Africa has to be noted:

Guideline 1.3.2:

"Good Manufacturing Practice is concerned with both production and quality control. The basic requirements of GMP are that:

(i) All manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing medicinal products of the required quality and complying with their specifications:

(ii) critical steps of manufacturing processes and significant changes to the process are validated;

(iii) all necessary facilities for GMP are provided including:

a) appropriately qualified and trained personnel;

b) adequate premises and space;

c) suitable equipment and services;

d) correct materials, containers and labels;

e) approved procedures and instructions;

f) suitable storage and transport;

(iv) instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided;

(v) operators are trained to carry out procedures correctly;

(vi) records are made, manually and / or by recording instruments, during manufacture, which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected. Any significant deviations are fully recorded and investigated;

(vii) records of manufacture including distribution which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form" (SADOH, 2005).

As the factors identified by the WHO and SAMRA concur with one other, these are briefly discussed as outlined in the SADOH (2005) GMP guideline.

3.2.3.2 Personnel

The South African GMP guidelines stipulate that in order to establish and maintain a satisfactory level of quality assurance and correct manufacture of medicinal products, reliance on sufficiently qualified personnel is imperative. Those persons are required / obliged to be familiar with and trained in GMP (SADOH, 2005).

The preferred structure used for personnel in a commercial environment is that of an all-encompassing dedicated staff; this is in fact virtually impossible in an academic setting. With their main business being education and research, the personnel in academic facilities are required to perform a wide variety of duties and, hence, staff is obliged to share responsibilities (Steel & Roessler, 1999). Thus, the training needs of the personnel at an academic facility should enable proficiency in all areas of the shared responsibilities.

Efficient planning and scheduling of activities within pharmaceutical pilot facilities is essential, due to frequent changes of the product and the scale of their demand. Planning and scheduling should address both long-term planning of resources and short-term scheduling of operations. With facilities already in place, "resources" in this instance refers mainly to the availability and allocation of skilled operators, engineers, chemists, etc. Scheduling of production activities in the pilot plant addresses issues of

efficiency and resource management (Mockus *et al.*, 2002). In commercial pilot facilities this could indeed present an ongoing challenge for skilled resources, whilst pilot facilities in academia invariably have to rely on the multi-tasking of their highly skilled staff and postgraduate students involved. Despite the perceived greater availability of the human resource element in academia, the pilot facility would still have to have its operations supported by adequate documentation, such as standard operating procedures (SOPs), protocols and operational programs that have been validated. These may then act as suitable support mechanisms for substitution with new staff.

3.2.3.3 Premises and equipment

The GMP principles set out for premises and equipment are such that they should be located, designed, constructed, adapted and maintained to suit the operations to be carried out. They should be designed so as to minimise the risk of errors, contamination and / or cross-contamination, and facilitate adequate cleaning (SADOH, 2005). Both in the academic and the commercial setting, the effect of environmental issues have to be taken into consideration when establishing any facility. However, for academic institutions undertaking these projects the challenge goes even further, due to the main "product" of these institutions being graduates, postgraduates and scholars, rather than drug products for clinical trials. The selection of a site for establishing a pilot facility in an academic environment is therefore far more challenging.

3.2.3.4 Documentation

Documentation is an essential component of GMP and includes: specifications, manufacturing formulae and instructions, procedures and records. This documentation should be free from errors and be written in a clear, unambiguous manner. In this way traceability of processes can be assured.

Due to the research-based nature of their pilot projects, academic institutions may have to evaluate their procedures more frequently than their industrial counterparts. For a facility manufacturing multiple products, these procedures may prove critical in keeping with the continuum of cGMP. This is especially the case if the design of the facility is constrained due to limited space or resources (such as availability of several mixing vessels or skilled technicians). Whilst SOPs and procedures are created to ensure process reproducibility, these may also be beneficial in ensuring that good

practices are adhered to where such practices cannot be incorporated into the existing facility design (SADOH, 2005).

3.2.3.5 Production

The actual production of the envisaged product must follow a process that should detail clearly defined procedures compliant with GMP, to ensure that the manufactured product is of the requisite quality. All areas (production, packaging, quality control and equipment) within the manufacturing facility must, of necessity, comply with current Good Manufacturing Practice.

The design or layout of the facility should essentially facilitate material and personnel flow within the facility that is consistent with GMP.

For the production process itself, SADOH (2005) gives the following guidelines for handling of materials and for personnel training:

i. Prevention of cross-contamination in production: The WHO defines cross-contamination as contamination of a starting material, intermediate product, or finished product with another starting material or product during production (WHO, 2005).

   This contamination may arise due to uncontrolled release of dust, gases, vapours, sprays or organisms from materials and products in process, from residues in equipment and from operators' clothing. These contaminants can be removed by means of:

   - efficient filtration of air supply;
   - dilution of contaminants; or
   - flushing of contaminants by supplying adequate ventilation (WHO, 2005).

   The risk of accidental cross-contamination can be minimised by:

   - adequate personnel procedures;
   - suitable premises;
   - utilising closed production systems;

- adequate, validated cleaning procedures;
- appropriate levels of product protection;
- correct air pressure cascade.

All in all, appropriate technical and organisational measures should to be taken to minimise the risk of cross-contamination (SADOH, 2005).

ii. Validation is done to ensure repeatability and consistency of a given process / procedure. This further reinforces GMP. Should there be any changes in the process, equipment, method, etc., these also have to be validated to assure that consistency in product quality is maintained (SADOH, 2005).

iii. Raw materials acquisition must be from those approved vendors named in the relevant specifications. It is essential that this received material goes through a goods receiving procedure, moves through the process of quality control and ultimately proceeds to raw material storage in a dedicated raw materials store. This store should be access controlled and dispensing of raw materials should take place as per prescribed production documents (SADOH, 2005).

iii. Processing operations of intermediate and bulk products: Before any processing takes place, it is critical to ensure that the workplace and equipment are free from any dirt or residues and have been validated as clean. The necessary processing conditions, as per the process requirements, must be adhered to. Any deviations from the accepted process must also be documented (SADOH, 2005).

iv. The purchasing, receiving, handling and control of primary printed and unprinted packaging material should be dealt with in a similar manner as raw materials. Specific attention should however be paid to printed packaging materials in terms of storage and distribution. Access to printed packaging must be strictly controlled. Reconciliation of packaging material after the packaging process is vital, especially where printed packaging material is concerned, to ensure that no loss, mix-ups or mislabelling has taken place. Dedicated access controlled storage is required for packaging materials. A procedure for destruction of old or redundant printed packaging material is necessary (SADOH, 2005).

v. When setting up packaging operations, a concerted effort must be made to reduce the risk of contamination, mix-ups and substitutions. Line clearance checks, attention to reducing contamination, adequate procedures and packaging process documentation, campaign production and packaging should also be scheduled if necessary (SADOH, 2005).

vi. The finished product must be quarantined until the conditions, as per the approved specifications, have been met. Upon successfully undergoing the necessary quality control tests, release of the final product to the finished goods storage area is then permitted (SADOH, 2005).

vii. Rejected, recovered and returned materials: Materials rejected and returned either to supplier or manufacturing facility should be clearly marked or labelled. The reprocessing of final or intermediate product is only warranted under exceptional circumstances and by authorised personnel only (SADOH, 2005). Procedures handling returns must define conditions according to which these goods are dealt with. Goods that have expired and have been rejected may not be reprocessed and must be destroyed according to a goods destruction procedure.

From the above adaptations of the South African GMP guidelines it is clear that the various operations for the prevention of contamination are each specific in their requirements with respect to GMP. The requirements of premises and equipment also reflect that the design of the facility and the equipment should be able to fully accommodate the operations of the facility. Hence, dedicated areas in the facility for these operations are necessary.

While following GMP guidelines to achieve the objective of producing medicines of quality, safety and efficacy, recognition is also given to the fact that there are alternative technologies that can be utilised, in achieving the required GMP compliance.

3.2.4 Containment

The required reduction of staff exposure to potentially harmful materials has resulted in the increased use of containment in production (Tovey & Baker, 1999). An increase in automation and safety considerations has resulted in increased use of air extractors and / or airflow units in production facilities. There are set standards and regulations that describe requirements for safe working practices and these have a major influence

on the layout and design of any facility (WHO, 2005). Process factors may also require specific manufacturing environments for the manufacture of these products, such as 'cleanrooms'.

A cleanroom has a *controlled* level of contamination that is specified by the number of particles per cubic meter at a specified particle size. Cleanrooms are classified according to the number and size of particles permitted per volume of air. Large numbers like "class 100" or "class 1000" denote the number of particles of size 0.5 µm or larger permitted per cubic foot of air. Various regulatory organisations have comparative grading systems, as is summarised in Table 3.1. The South African regulatory authority accepts references to all these classifications. However, the most commonly used are the ISO (International Organisation for Standardisation) classifications.

Table 3.1 Comparison of different airborne particulate classification systems for clean areas (adapted from WHO, 1992).

WHO (GMP)	United States (customary)	ISO/TC (209)	EEC (GMP)
Grade A	Class 100	ISO 5	Grade A
Grade B	Class 100	ISO 5	Grade B
Grade C	Class 10 000	ISO 7	Grade C
Grade D	Class 100 000	ISO 8	Grade D

Legend:
EEC: European Commission; ISO/TC: International Organisation for Standardisation Technical Commitee.

The product and process requirements determine the extent of containment that is required. The required level of protection may have to be that of a "cleanroom" as described above. Cleanroom conditions are required in cases of aseptic processes or where sterile manufacturing conditions are prescribed.

Three levels of protection are described in the ISPE (1996) guideline on facility design:

- Level 1 - General. An area with normal housekeeping or maintenance. In this area no air filtration is required for the product. Air filtration to protect coils in air handling units (AHU), both for occupants and to facilitate housekeeping is recommended. A minimum of 30% filtration is recommended. Some sites may require higher filter efficiency and dust holding capacity due to natural airborne material such as pollen, coal, quarry dust and combustion exhaust particles. Level 1 protection can be equated with ISO 9 conditions.

- Level 2 - Protected. An area in which steps are taken to protect the exposed product and materials, which could become part of the product. These steps may only be procedural.

- Level 3 - Controlled area is an area in which specific environmental conditions are defined, controlled and monitored to prevent degradation of the product (or materials which will become part of the product).

With level 2 and level 3 protection areas, 85% dust spot efficiency filters are recommended. If air is returned to the heating, ventilation and air conditioning (HVAC) system, a 99,9% high efficiency particulate air (HEPA) filter in the supply or return duct system would generally provide adequate protection against cross-contamination between exposed products or materials. If a HEPA filter is critical in preventing cross-contamination, it should be tested regularly for specified containment. If failure of the primary HEPA filter would jeopardize the product integrity, a backup HEPA filter should be considered. HEPA filtration is not adequate for vapours and return air streams carrying hazardous or detrimental vapours. If HEPA filters are utilised on a supply air system, periodic testing is recommended to confirm proper particulate containment. This testing can generally be of a total air stream type and scan testing of the entire filter face would not be required (ISPE, 1996).

Level 2 and 3 protection can be equated with ISO 8 or 7. Table 3.2 provides a correlation between the GMP requirements for various areas in a facility and the approximate ISO class equivalent. The choice of areas in Table 3.2 are limited to the areas of concern in this study.

Table 3.2 Correlation of GMP requirements and respective ISO classification (ISPE, 1998 & WHO, 1997).

Area concerned	GMP requirements (Level of protection)	Approximate ISO class equivalent	Protective dress code
Canteen, street	External	External	None
Receipt and despatch	Unclassified or Level 1	ISO class 9	Appropriate to the area
Warehouse and offices	Unclassified or Level 1	ISO class 9	Appropriate to the area
Weighing and dispensing	Level 2 if enclosed Level 3 open product	ISO 8 if enclosed ISO 6 or 7 open product	Clean garments
Blending	Level 2 or 3	ISO 8 or 7	Clean garments
Primary packing	Level 2 or 3	ISO 8 or 7	Clean garments
Secondary packing	Level 1	ISO 9	Clean garments
Non-sterile processing	Controlled or class 100 000 (while operative)	ISO 8	Clean garments
Rooms where filling takes place	Controlled or class 100 000 (while operative)	ISO 6 or 7	Sterile garments
Change rooms and airlocks	The same class as the area they serve	The same class as the area they serve	Change of garments for higher classifications

3.2.4.1 Manufacturing environments

Manufacturing in an ideal environment should not only lead to better quality products but should also result in improved production rates and provide better operator comfort, satisfaction and safety. The WHO (2005) draws particular attention to the manufacturing environment, which encompasses personnel, product and environmental protection.

In order to ensure a safe and productive manufacturing facility, it is essential that these three primary considerations are addressed in the design of any manufacturing facilities. Figure 3.2 shows how a cascade of factors, originating from the primary considerations, influences GMP in the manufacturing environment (WHO, 2005).

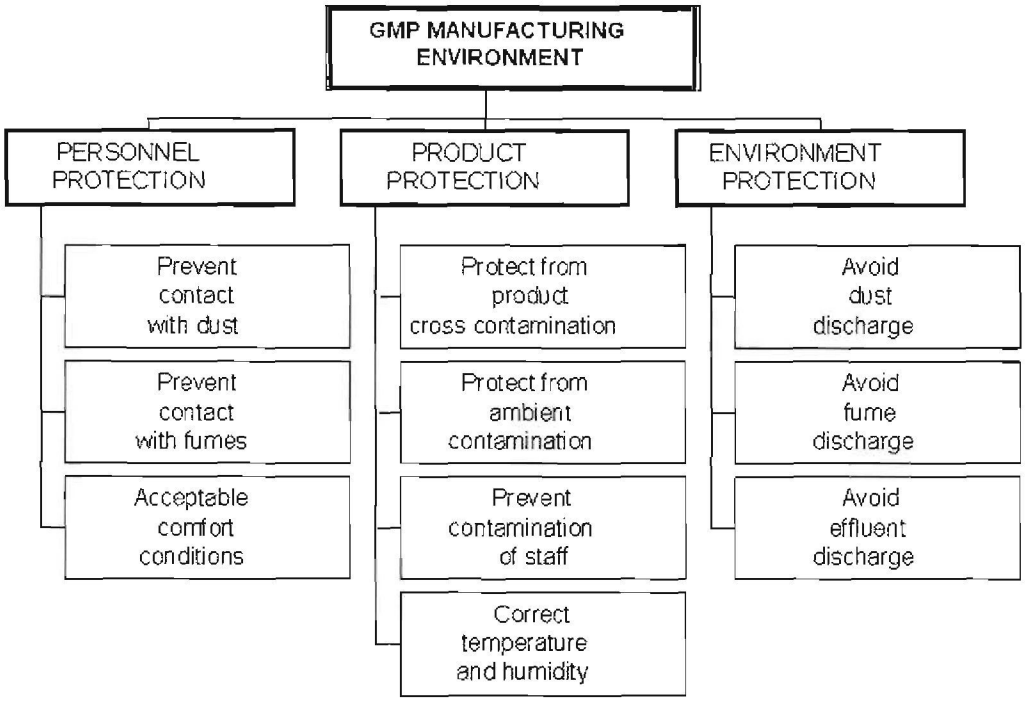


Figure 3.2 Factors that influence the manufacturing environment, as adapted from WHO (2005).

The South African guidelines for GMP state that: "Products intended for use in clinical trials (late Phase II and Phase III studies) should as far as possible be manufactured at a licensed facility, e.g. a pilot plant primarily designed and used for process development" (SADOH, 2005). This same requirement has to be applied in the case of a pilot production facility in an academic environment. The need to ensure GMP compliance may include provisions in both the design and in procedures that would allow for the sharing of spaces, and for optimal use of trained and qualified personnel.

Two factors that significantly affect the manufacturing environments are:

i. Materials management: The receipt, handling, storage and dispensing of raw materials, in-process product, bulk final product and finished final product should conform to cGMP principles. Dedicated areas, prevention of contamination and cross-contamination, use of approved raw materials in production, sampling, etc., are components of good manufacturing practices that can dictate, to a large extent, the design of the facility, and locations and

characteristics of various dedicated areas (SADOH, 2005). Analytical testing of raw materials, in-process and final product have to be conducted according to current GLP standards.

ii. Equipment: The nature and type of equipment used in a facility contribute essentially to the layout of the facility. Production process, dedicated areas, clean-in-place systems as well as equipment all contribute to the decision on how to design the facility to best accommodate the cleaning process as well as the processing and technology involved in production.

3.2.5 Techniques and technologies to achieve GMP

Facility design has progressively evolved over the years to engage the field of engineering.Technological advancements have been incorporated and is ultimately moving towards complete automation and reduced contamination. GMP has also been achieved through the use of non-GMP technologies such as HVAC, to ensure containment. Non-GMP technologies also need to be considered in facility design, as many of these provide infrastructure that may pertain to the occupational health and safety of the operators, as well as work environment requirements.

The ISPE (1996) guide for new and renovated facilities lists the following on alternative and non-GMP technologies:

3.2.5.1 Product and processing considerations

When designing a new manufacturing facility, the product/s to be manufactured in this facility must be defined and characterised. Properties of active ingredients or product composition can provide challenges to the manufacturing operation and its ability to comply with GMP regulations. Addressing these challenges early in process development and facility design can lead to long-term savings. Processing considerations are usually reviewed in the order in which they normally occur in a manufacturing operation.

3.2.5.1.1 Product characteristics

i. Toxicity / Potency: Process development and facility design should be coordinated to allow the most effective handling of toxic compounds. Overall process flow and each manufacturing step should be evaluated for toxicity levels, as it is not uncommon for the danger to decrease during the manufacturing process, either by dilution or by a change in the physical characteristics. The level of facility engineering necessary to protect operators

and other products may in some cases be decreased throughout the manufacturing procedure. For example, HVAC requirements designed to handle the bulk drug product during weighing operations may not be needed in the filling stage. However, the concept that these processes generate less dust as they progress cannot be generalised. The level of dust containment and generation of each operation and equipment type needs to be considered in facility design and equipment selection (ISPE, 1996).

ii. Physical properties: The physical properties of an active ingredient or drug product should be evaluated at each step during the manufacturing process. Characteristics to consider include physical state, density and particulate nature. Materials with low density and high probability of becoming airborne require enhanced dust collection and, possibly HVAC design. Liquid formulations may not require much, if any, specialised engineering as they are easy to control and can be diluted quickly during processing. Granular and free flowing materials may be contained more easily than poorly flowing solids (ISPE, 1996).

iii. Hygroscopicity: Products that absorb moisture and as such, become unstable or difficult to handle, require special process and facility features. Low humidity environments may be necessary. This would affect not only HVAC requirements but also the requirements for room fit and finish. Proper process design may lead to lower facility costs. Avoiding open processing, by using suitable manufacturing equipment and material transfer, may be more cost effective than addressing room environment. Moisture sensitive products are generally sensitive throughout the process and may require protective measures throughout (ISPE, 1996).

iv. Cleanability: Usually a function of product solubility, the ease with which a facility is cleanable, affects facility design and selection of equipment. Effective clean-in-place system design requires uniformity in cleaning systems, cycles and procedures. Active ingredients as well as specific excipients such as binders, lubricants and coating systems, (which tend to be difficult to remove) should be included in the cleaning evaluation (ISPE, 1996).

v. Light sensitivity: Many active ingredients may degrade when exposed to normal white light. Complete exclusion of light, to prevent decomposition due to photochemical reactions may be necessary. Closed processes and equipment

can be designed to avoid light exposure during manufacturing or alternative light sources like infrared may be used. If degradation occurs only after prolonged exposure, light exclusion may not be necessary. However, appropriate time limitations on production must be established (ISPE, 1996).

vi. Sensitisation: With continued exposure to some products, operators may become sensitised, causing allergic reactions. Sensitisations are usually unrelated to potency. GMP requires the use of dedicated or separate manufacturing facilities for highly sensitising agents, such as certain antibiotics. In these cases, protection of operators from the product is critical (ISPE, 1996).

3.2.5.1.2 Process considerations

It is of critical importance to consider or evaluate processing alternatives against GMP, economic process, facility and other considerations. These are determinants in decisions pertaining to specific design and cost saving opportunities.

Table 3.3 provides an outline of areas that could generate problems within the facility and that should be considered during the design phase. The keys for interpretation of the colours are given below the table. A description of relevant factors follows after the table.

Table 3.3 Process considerations for facility design (adapted from ISPE, 1996).

PROCESS				
		Throughput	Yield	Change Over
Weighing	Conventional	Green	Green	Green
Dispensing	Laminar Flow	Green	Green	Green
	Isolator	Red	Green	Red

FACILITY							
		Space requirement	Containment	HVAC	Dust collection	Architectural finishes	Process Utilities
Weighing	Conventional	Green	Red	Red	Red	Red	Green
Dispensing	Laminar Flow	Green	Yellow	Yellow	Yellow	Yellow	Green
	Isolator	Red	Green	Green	Green	Green	Yellow

Key:

Red: This is an area that requires specific attention, increased effort and potentially increased design, construction or operating costs.

Yellow: This is an area that must be considered as to its impact on facility design.

Green: Problems are not likely to occur. Significant opportunity exists for savings in design, construction and operating costs may be found.

The relevant factors that are considered:

i. Weighing / dispensing: Table 3.3 shows issues for consideration once the type of equipment has been determined. As an example, the initial capital investment for a multi-product isolator may be prohibitive. However, the use of isolators in the weighing / dispensing operation reduces the likelihood of problems in terms of cleanability, cross-contamination, containment, room HVAC and architectural finishes requirements with associated cost savings. However, the trade off is specific attention, and increases in effort, costs of validation, cost of equipment, throughput, changeover and space requirements (ISPE, 1998).

ii. Mixing / blending: Whilst the equipment design and requirements for mixing / blending are relatively simple, the primary concerns are the initial equipment costs and facility requirements, such as floor space and utilities. Space requirements will vary with the size and type of the unit. Possible processing trade-offs are available, and each has to be examined on a case-by-case basis (ISPE, 1998).

iii. Finished dosage forms: Generally, completed bulk liquid oral dosage forms may offer challenges with respect to contamination and bulk storage. Special consideration should be given to the filling equipment used, the need for additional caution in the process, and architectural changes or selection of filling equipment required to minimise contamination (ISPE, 1998).

3.2.5.2 Architectural considerations

The selection of materials and finishes to provide the correct level of protection is affected by product and material flow, personnel flow and waste flow in the manufacturing environment (ISPE, 1996; ISPE, 1998 & SADOH, 2005). The effects of these are discussed below.

3.2.5.2.1 Product and material flow

Key layout design criteria associated with material flow and building layout include:

- providing logical, direct and sequential flow, minimising the potential for confusion;
- minimising movement distance;

- providing adequate protection against contamination;
- minimising material handling steps; and
- providing adequate staging and access.

The cost of providing the proper level of protection to achieve the above must be considered in relation to contamination risk and level of efficiency.

The facility for liquid dosage forms does not need a one-way material or product flow to protect against contamination. However, special consideration should be given to multi-product facilities, where it may be advisable to separate material and product flows, unless the material or product has been placed in a package or container to prevent contamination or mix-ups (SADOH, 2005).

Both personnel and the environment may be at risk from exposure to open material or product flow. Flow patterns should prevent transport between processing areas or operations in open containers and operations prior to appropriate cleaning. Physical barriers or signs should prevent unprotected personnel from entering areas where they could be directly exposed to the material or products (ISPE, 1998).

The areas of attention involving storage, handling and transfer of products and materials are discussed below.

i. Warehousing: Raw materials, components and finished goods (both quarantined and released), may require warehousing and storage. Storage of rejected or returned goods also need to be considered. Specialised, independent storage may be needed for certain materials, due to their environmental requirements, health or safety hazards, or regulated status. Selection criteria of the type of warehousing and material storage is influenced by the amount of storage space required, the storage space available, the throughput requirements, costs of operation and construction costs (ISPE, 1998).

ii. Material handling: The equipment and costs associated with automated transfer of materials should be weighed against the benefit of greater efficiency. Bins may be used to transport materials through areas with a lower level of protection than the manufacturing space itself. Manual and automated transfer is acceptable as long as adequate control is in place (ISPE, 1998).

iii. Material tracking: Minimising the risk of materials being confused is essential. Specific considerations include the need for dedicated staging or storage areas, the use of fixed versus movable partitioning (e.g. ropes, chains or mesh fencing), clear identification of containers, bar coding for identifying materials, and the storage conditions required for different materials, e.g. temperature, humidity, safety and regulatory requirements (ISPE, 1998).

iv. Clean and dirty corridors: A clean corridor arrangement to control the level of contamination risk associated with a facility manufacturing oral liquid and topical dosage forms is not usually required. Contamination issues can be addressed through a variety of alternative methods, including direction of air flow, dust control, contained transfer, cleaning and operating procedures (ISPE, 1998).

v. Segregation and containment through airlocks: Decisions on these matters should be based on the level of protection required in terms of safety and environmental considerations. Airlocks should be used in cases where other methods such as directional airflow and dust control procedures are not deemed to be effective (ISPE, 1998).

vi. Containment devices and micro-environments: With highly potent or toxic products, gowning, airlocks or rigid procedures may not provide the required level of operator or environmental protection. In this situation, establishing a micro-environment may be necessary. However, micro-environments are generally not required in a liquid dosage form facility, as isolation or containment of the product does not warrant such a level of complexity. Having to deal with airborne particles with oral solid dosage form manufacture is a different matter (ISPE, 1996; ISPE, 1998 & SADOH, 2005).

vii. Controlled substances: Personnel movement and access to certain areas and secured stores containing substances requiring regulatory control need to be addressed in the facility layout.

3.2.5.2.2 Personnel flow

Personnel flow should be developed to protect the product, personnel and the environment, while addressing site security and control issues. Regardless of the level of protection required, an oral liquid and topical dosage form production facility does not need a one-way personnel flow to protect against contamination. Where

appropriate, procedures to prevent contamination must be put into place. A change of clothing would be required, for example, between a dusty operations area and a level 3 area (ISPE, 1996).

Segregated entrances and exits may be necessary to protect against contamination and to allow for gowning or decontamination procedures. If one access point is used as both an entrance and an exit, simultaneous entrance and exiting should not occur. Acceptable methods for preventing this include administrative controls, interlocking of doors and signalling systems such as lights, indicating gowning, decontamination or other activity being in process.

The design criteria for efficient movement of personnel, while maintaining control and segregation, include:

i. Segregation and control of personnel type: Controlling personnel flow by type (operator, employee, visitor or service) may offer product and personnel protection as well as security advantages. Methods include using badges, uniforms and procedures.

ii. Gowning and de-gowning: This may be required to protect the product, operator or the environment. If gowning is necessary, a progression from general to specific change areas should be considered. Areas where potent or toxic material is handled may need separate gowning and de-gowning rooms. De-gowning operations should also not violate the cross-contamination control conditions achieved in commonly used areas. Procedures should also address employee movement to facilities and areas such as toilets, the cafeteria and offices.

iii. Personnel protection: In addition to the primary protection provided by process and system design, secondary measures such as contained breathing air systems or air / water showers, specific to the area of hazard, should be considered.

3.2.5.2.3 Waste flow

Waste flow should not contaminate the process it is derived from or serve as a source of cross-contamination to other areas. Waste can be broadly classified as follows:

i. Innocuous non-product waste: This is created outside of the process environment where product exposure is not a concern. Examples include

packaging and shipping trash generated at receiving docks. No special treatment or handling is required.

ii. Product-contaminated waste: This includes materials that have entered the process areas where products or materials may be exposed. Product-contaminated waste should be controlled by procedure, process or transport design. The key concerns are to guard against waste entering into the production process. Product waste should also be controlled in such a manner as to not cross-contaminate other areas or processes.

iii. Hazardous or regulated waste-materials requiring specialised storage or disposal: These include solvents and potent / toxic materials. Hazardous or regulated wastes should be handled, collected and stored in a manner that adequately addresses safety, health or environmental concerns and complies with applicable codes and regulatory requirements.

Packaging labels and other peripheral materials may require additional handling or processing, for instance the need for reconciliation of the number of labels issued against the product runs to confirm quantity control and tracking.

3.2.5.2.4 Product / personnel protection

Architectural features and design need to provide the appropriate level of protection for closed processing systems, micro-environments and handling of increasingly toxic materials (ISPE, 1996).

3.2.5.2.5 Materials finishes

Performance criteria for durability, cleanability, functionality and maintainability should be established. These are used to select the finish and substrate materials that successfully meet the performance and cost requirements. Finish requirements and detailed elements of architectural designs depend on the level of protection required. The following aspects have to be considered:

i. Cleanability in a level 1 protection area requires regular removal of debris such as papers, cardboard, etc. by dusting and sweeping.

Cleanability in a level 2 protection area requires access to primary surfaces, which are those solid surfaces closest to an exposed product. In a room this would include the walls, floors, ceilings and doors, the room-side of air diffusers and drain covers in the floor. Isolation barriers or enclosures around the

exposed material may provide these primary surfaces. In such cases room surfaces would only require level 1 protection.

Cleanability in a level 3 protection area is similar to that required for level 2 areas. However, more regular wipe down processes would be expected. Surfaces in these areas should be non-porous and smooth that minimise areas of dust collection. Coved intersection details and integral floor bases will enhance cleanability. Horizontal surfaces must be accessible for cleaning (ISPE, 1996).

ii. Durability is most important in areas where degradation of finishes can cause product contamination. All finishes selected should be able to withstand the traffic they are expected to bear. The need for maintenance, repair or replacement must be kept within acceptable limits. Finished floors must be able to withstand the rolling wheel load of forklifts, pallet jacks and mobile vessels. Chemical resistance to process ingredients and cleaning materials, particularly solvents and particulate stains, must be considered (ISPE, 1996).

iii. Functionality: Specialised functions independent of, or unrelated to, product exposure and contamination risk are often required of a finished system. For example, providing acceptable air pressurisation, maintaining low humidity conditions, conductivity or anti-static requirements may depend on the finish, substrate and detail. In some cases the need for anti-microbial considerations may be of concern when selecting materials and finishing systems (ISPE, 1996).

Other factors affecting selection of materials and finishing systems include the ease of transition to adjoining surfaces, repair, renovation and / or replacement, and which may require regular maintenance procedures. In general, the less disruptive and involved the repair effort, the better the finish will serve, both to maintain architectural requirements and to meet the needs of the manufacturing operation (ISPE, 1996).

iv. Cost effectiveness: The type of finishing should be selected based on performance criteria. High cost finishes may provide the best performance and aesthetic conditions but cost more than necessary for minimum performance requirements. In considering cost effectiveness, both initial cost and the likely need for repair or the impact of renovation and alterations needs to be taken into account (ISPE, 1996).

3.2.5.3 Process support and utility systems

Any manufacturer should review the utilisation of systems within the facility and determine the category or categories into which they fall, in order to provide a basis for determining the design, construction and commissioning requirements for the system.

The cost / benefit ratio derived from installing separate utility systems or distribution networks, versus special treatment at points of use, should be considered in the design. For example, a compressed air system can be used as both a process and a utility system. If there are many process uses, it may be economically justified to run separate distribution systems throughout the facility. If only a few process uses are required / necessary, then utilising a general utility system with point-of-use filters and stainless steel piping after the filters at process-use points may be the more economical design (ISPE, 1996).

3.2.5.3.1 Process systems

Process systems are considered to be critical. They have to be designed, constructed and commissioned to provide material that meets a defined specification (considering product quality requirement) and prevents contamination. An example of this is process water passing through piping. The nature of the fluid being conveyed must be considered when selecting materials for storage and for distribution systems. For non-corrosive fluids such as nitrogen, typical materials include copper, plastics and stainless steel. Construction methods may leave a residue on the interior surfaces of the piping involved, which could lead to product contamination (ISPE, 1996).

3.2.5.3.2 Process support systems

Process support systems are considered to be non-critical. However, its effect upon the manufacturing process should be considered from a commissioning point of view. Pressure alarms (low or high), for example, can be constructed and installed according to GMP compliance.

3.2.5.3.3 Utility systems

These systems are also considered to be non-critical and are designed in accordance with GMP guidelines.

i. Process water

- Water used in the manufacture of oral dosage forms should be of a pharmacopoeial grade (e.g. USP purified water) and meeting all the

requirements of the relevant pharmacopoeia. Additional information regarding the general design, construction and commissioning of treated water systems should be considered during any facility design (ISPE, 1996).

- Flexible hoses may be used to convey process water from a distribution piping system to point of use. Hose material, contact surfaces and contact time of the water with the hose material has to be taken into consideration. Water should either be prevented from accumulating in the hose after use, or be flushed out of hose before the next use. Any accumulated contaminants in these water hoses would cause contamination further along in the process (ISPE, 1996). Direct connections to process or equipment should be designed to prevent reflux (back) into the process water system. It should be possible for each point of use to sample the water through the outlay itself, or via a sample valve (ISPE, 1996).

- Pharmacopoeial grade water could also be conveyed in bulk containers. Pharmacopoeial specifications for construction materials, as well as storage time, should be adhered to. Acceptable materials include stainless steel and high density poly-ethylene (HDPE) (ISPE, 1996).

ii. Cleaning water: The cleaning water for the facility and equipment is selected according to the relevant process requirements (ISPE, 1996). The cleaning water should also meet the requirements for drinking water (potable) in South Africa.

3.2.5.4 HVAC

These systems focus on assuring the control and monitoring of GMP-critical parameters and this differentiates them from other design requirements. Factors such as schedule, budget, reliability, economic analysis criteria and future growth / flexibility should be taken into consideration when deciding upon the most suitable HVAC system for any given application that will ensure GMP compliance.

A less sophisticated and less expensive HVAC system may suffice for GMP compliance if used concurrently with other technologies such as isolation / barrier systems or closed processing systems (ISPE, 1996).

3.2.5.4.1 Process Definition

The following criteria need to be determined (ISPE, 1996):

i. Critical room parameters that affect product materials;

ii. Acceptance criteria for room parameters;

iii. Which processes have the potential to contaminate the product by airborne matter, or to expose the product to factors exceeding critical room parameters e.g. temperature or humidity;

iv. Processes or operations not affected by room environment conditions for any of the following reasons: The product or the material is isolated from the room in an enclosure or vessel; the operation is of such short duration that room environment conditions will not appreciably alter the conditions of the product or material; and / or the degree of exposure is such that it does not adversely affect the product or material;

v. Potential sources of room contamination, which may include:

- Airborne contaminants and the make up of the air;
- Process equipment / operations;
- Room construction materials;
- Outdoor floor drains;
- Failure of HVAC system with reversal of flow;
- Transportation equipment and containers;
- Personnel;
- Multiple products / materials in the facility, especially with potent or toxic compounds.

3.2.5.4.2 Critical parameters

"Out-of-specification" temperature, humidity and airborne particulate matter are critical room parameters that may affect products or materials. Please check. Microbial contamination must also be taken into account. Air changes and room pressure are

usually not critical parameters. However, the relative direction of airflow between spaces may be a critical parameter if airborne particles or vapour could have a detrimental affect on products or material in other areas / spaces (ISPE, 1996).

3.2.5.4.3 Temperature

Room temperature may be a critical parameter for both open and closed operations. Most products, materials and processes can handle a wide range of temperatures. However, the width of this range decreases as the exposure time increases. For example, the contents of a large processing vessel would not measurably change temperature during typical sampling activities. If products or materials were stored or exposed for significant periods, such as in a non-temperature-controlled blender, then significant effects may occur. Actual product temperature monitoring could be performed as an alternative to room temperature monitoring (ISPE, 1996).

3.2.5.4.4 Relative humidity

i. The relative humidity (RH) in the room may affect exposed products or materials sensitive to moisture. RH levels generally have negligible effect on aqueous products. However, liquid products can lose moisture to a low humidity room over an extended period. Typically, exposed humidity-sensitive products require humidity controlled to 30-50% (ISPE, 1996).

ii. If dehumidification is required, the system selected should not contaminate the product. Cooling coil-type systems generate large amounts of condensate, which must be properly drained to avoid microbial contamination. Liquid and dry-type desiccant systems should be evaluated for potential carry-over of desiccant into the supply air stream and its effect on the exposed product (ISPE, 1996).

3.2.5.4.5 Airborne particulates

The ISPE (1998) baseline guides for new and renovated facilities indicate that:

i. In contrast to aseptic processing, there appears to be no prescribed particulate classification for oral dosage form facilities. Classification is determined by the nature of the product, the product process and the materials used in production.

ii. Cross-contamination can originate from both the internal environment and from the outside. In all air handling systems, the filtration should be evaluated for adequate arrest of outdoor particulate matter. In recirculation systems, the filtration must be evaluated for cross-contamination of the product and for general house-keeping particulates. If the facility produces multiple products and some of these products have a zero tolerance level for cross-contamination with other products (e.g. penicillin), then air from these spaces / areas should not be returned (even if HEPA filtered), to those areas/spaces not tolerating this type of contamination.

iii. In a facility where multiple products are exposed, dedicated air handlers and ductwork may be more practical and cost-effective. Capital costs would be higher, but filter maintenance and ongoing testing costs should be lower. The efficiency of air filtration should be proportional to the potential for contamination. The requirement for supplying filtered air depends on the level of protection needed, but should meet minimum indoor air quality (IAQ) standards.

3.2.5.4.6 Room relative pressure and air change rates

i. Room relative pressure may be a critical parameter if:

- it is a multi-product building, where some or all of the products are in dry form, exposed to room air without barriers, or can become airborne and migrate by air to other product areas.
- high enough concentrations of airborne product, materials or contaminants can pose an exposure threat to operating personnel. (When this occurs, both personnel and products exposed in the facility could be at risk.)
- adjacent spaces are controlled bi-directionally, i.e. airborne migration of particles in either direction can be controlled (ISPE, 1996).

ii. There is no quantified requirement for relative pressurisation. The velocity and direction of airflow between spaces should be adequate in order to reduce the counter flow of airborne particulate matter or vapour contaminants to spaces where airborne cross-contamination is of concern (ISPE, 1996).

iii. Pressurisation should be set up to reduce airborne particulate matter from passing from the outdoors, from above ceilings, mechanical or similar spaces and from level 1 protection spaces to level 3 protection processing spaces. Airlocks or buffer zones can be used to separate production areas from adjacent common corridor / staging areas, non-controlled areas and potent drug manufacturing areas.

iv. When the doors are closed, room pressure should be demonstrably positive or negative. Airlocks or buffer zones can provide additional protection, if only one door is opened at a time. Pressured airlocks could have either positive or negative relative pressure, depending on the requirements for a particular situation (ISPE, 1996).

v. Prior to air balancing, rooms should be inspected for obvious leakage and for architectural integrity. Leakage may have a significant effect on the room air balance and / or upon the ability for particulate matter to enter or exit any space/area (ISPE, 1996).

vi. There is no minimum GMP requirement for air changes per hour, with the exception of aseptic processing. Air flow into and out of a space should be based on providing the required cooling, heating, relative humidity, pressurisation, particulate control, dilution ventilation, recovery time from an upset (spill or dust emission) condition and non–GMP codes. These factors generally result in air change rates of between 4 and 20. However, rates higher than this have also previously been used to reduce the number of particles per square metre (ISPE, 1996).

vii. Regular monitoring of critical points should indicate to the user when acceptance criteria are not being met. If alert points are being utilised, these would indicate when a monitored parameter is beginning to drift out of control (ISPE, 1996).

3.2.5.4.7 Special processes

The ISPE (1996) baseline guide emphasises the following on special processes:

i. Certain processes, such as dispensing, have the potential for product cross-contamination as well as posing a risk to the operator. If a product, its materials or its components are to be exposed to the room, airflow away from the operator towards the product will minimise the risk to the operator. However, to

protect the product from contamination, it may be necessary to provide the operator with special gowning or to arrange the work-stations in such a manner that neither the product nor the operator is exposed to the other (via the airflow pattern). Air filtration needs to meet product requirements. The potential for cross-contamination should be evaluated and enclosed dispensing could be considered, in order to obtain a reduction in the required level(s) of protection.

ii. The use of an isolator or barrier such as glove box or glove bag reduces the volume of environment to which the process is exposed, often with significant reduction in HVAC size and cost (ISPE, 1996).

3.2.5.4.8 Worker comfort

i. Maximum and minimum room temperatures and humidity should be within the limits specified by the environmental regulations for workplaces of the Occupational Health and Safety Act. This Act provides that should the exposure in terms of the time weighted average index, as determined over a period of one hour, exceed a value of 30 in the environment in which an employee works, the employer of such an employee shall take steps to reduce the said index to below 30. However, in cases of lower temperatures the maximum exposure periods should be observed. Conditions may thus have to be adjusted for workers in protective clothing (SADOL, 1987).

ii. A range of 25% to 60% RH is recommended for worker comfort where occupancy is continuous. However, since some facilities will have 100% outdoor air systems, the need and cost of comfort dehumidification needs to be considered in the light of the process requirements and worker comfort (subject to time exposure).

iii. Very low humidity can lead to:

- malfunctions or problems in some office, packing and electric equipment;
- a rise in potential static discharges;
- an increase in dust clinging to surfaces;
- an increased generation of particulate matter from dry skin.

iv. High humidity increases corrosion and can enhance microbial growth in spaces and building materials.

v. Workplace noise levels should be addressed, especially where local or portable dust collection systems are used (ISPE, 1996). The environmental regulations on noise level stipulates that no worker be exposed to an equivalent noise level equal to 85 dB or higher (SADOL, 1987).

3.2.5.4.9 Air systems

i. The probability of product contamination can increase with recirculation of unfiltered air from one space to another. Without filtration or local capture and control, recirculation will increase the levels of particulate, flammable and / or toxic airborne materials. Returning this air to the air-handling unit is feasible and economically justifiable, as the air handling system would save energy on air that has already been conditioned.

ii. The proximity of outdoor air intakes and mechanical equipment rooms to HVAC exhaust or process vents can be a major factor for consideration in building layout and design. Exhaust and vent stacks (including process system discharges) should be kept as far from intakes and as high as is practical, to minimise cross-contamination.

iii. Where exhaust air contamination is an environmental issue, exhaust stream treatment must be considered. There is usually a lifecycle cost advantage in minimising the volume of exhaust air by means of process isolators, point exhaust hoods and enclosed processes.

iv. Airflow patterns should be evaluated for potential product contamination, effective distribution, and mixed or unidirectional flow as required, and for adequate dilution and contaminant removal. Piping or electrical fixtures should not adversely disrupt airflow patterns or devices, process equipment, material transport equipment, people or opening and closing of doors.

v. Separate systems should be considered for recirculation systems that serve multi-product areas and where some of these products have little or no tolerance for cross-contamination with other products e.g. penicillin, steroids, etc.

vi. Emergency requirements should include:

- pressurisation of exits and/or a fire alarm;
- a smoke purge or smoke control system;
- emergency ventilation and smoke control; and
- an air system operation in the event of a hazardous spill.

vii. Dust collectors should generally be located outside of buildings. However, they may be located inside a building if they are installed adjacent to an exterior wall and vented to the outside through a straight duct with explosion vents and do not exceed 3 m in length (ISPE, 1996).

3.2.5.5 Electrical systems

Most electrical system layout, circuiting and insulation specifications in an oral dosage form facility are not critical. The ease with which electrical equipment, lighting fixtures and electrical devices are cleanable, is the primary GMP concern. However, room pressurisation and its effect on contamination risk through conduits and openings to adjacent spaces should also be considered, in defining the level of protection required. Although not a strict GMP requirement, the manufacturer may consider the cost benefit of enhanced system reliability (for example, emergency power to control systems) and the colour rendition and intensity of light, as these may affect light sensitive products or product inspection (ISPE, 1996).

As electrical system specifications are not critical in oral dosage form manufacture they do not directly influence the finished product specification. Some components of electrical systems that need to be considered include:

i. Power distribution: Although the power system's specifications are not critical, it is important that it has to be reliable. Loss of power or poor power quality for a critical piece of equipment or an instrument may affect product quality and lead to product rejection. Power distribution may affect the location and type of equipment and should be considered in conjunction with the protection requirements. For example, it may be desirable to recess a power receptacle for to promote ease of cleaning.

Another example for both cost and ease-of-cleaning considerations, is the location of both class 1 or class 2 electrically rated light switches in corridors

outside of process rooms or in other electrically non–classified rooms. This would allow for the use of less expensive switches rated for general-purpose use, which are easier to keep clean, or which have been moved to an area where ease of cleaning is less of a concern. These advantages should be weighed against convenience to the operator, especially if it involves leaving a controlled area to manipulate a switch (ISPE, 1996).

ii. Lighting: The ISPE guidelines stipulate the following considerations for light fittings:

- The colour rendition and intensity of lighting equipment used for inspection, cleaning or viewing of calorimetric titration may be considered critical. If so, they should be considered in conjunction with the inspection, cleaning or maintenance of equipment.
- Proper rating of all light fixtures for electrical classification and surface temperature is required for the facility.
- The lighting fixtures used in level 2 and level 3 protection areas should facilitate easy cleaning and should be able to withstand the pressure and temperature of any water streams used for wash down. In order to do this, it may be necessary to use glass instead of plastic shields.
- Fixtures used in a level 2 protection area should generally not be located above exposed products (or materials which may become part of the product) so as to prevent contamination from dislodged accumulated dust. Lighting fixtures used in level 3 protection areas should be arranged and designed to prevent any accumulation of dust or foreign materials. Flush mounted fixtures; recessed fluorescent fixtures or teardrop designed fixtures may be appropriate.
- Emergency lighting should be included (ISPE, 1996).

iii. Communication systems: Communication equipment used in protected areas should be designed to enable easy use and easy cleaning. Communication equipment should be arranged such that accumulation of dust or foreign materials is prevented. For instance, paging systems should be recessed into

the wall or ceiling, especially for an area requiring level 3 protection. Communication systems may have an effect on some electronic equipment, which may be considered critical in isolated cases.

3.2.5.6 Instrumentation and controls

The envisaged pilot facility design only includes production of the product, whilst the analytical testing will be conducted by a contract analytical laboratory at the Potchefstroom campus of the NWU, the Research Institute for Industrial Pharmacy (RIIP). The Quality Assurance Unit of the manufacturing facility will inspect the contract analytical laboratory. The Institute is accredited by the WHO and has cGLP status.

The instrumentation and systems used need to be validated. Instrumentation used in production and processing has to be calibrated and be compliant with GAMP (Good Automated Manufacturing Process) (SADOH, 2005).

3.2.5.7 Cost considerations

Although there are a number of HVAC, architectural and procedural approaches by which to meet facility requirements, it is likely that there will be one combination of these approaches that provides the lowest facility life-cycle cost. Risks and benefit factors identified in the ISPE (1998) guide which need to be considered in a life-cycle cost analysis include the following:

i. The use of isolation barriers rather than letting the product be exposed to the room environment. Physical barriers can significantly reduce HVAC requirements, reduce product exposure and improve process quality, but may place operating and cleaning burdens on the facility user. Barrier / isolator technologies can provide solutions to some GMP, worker safety, building safety and environmental protection problems.

ii. Worker protection options include barriers or capture devices, personal protective equipment or dilution ventilation to ensure safe airborne concentrations. These measures apply both to product exposure and flammable materials.

iii. Cross-contamination prevention options include once-through ventilation return air with filters to capture product contaminants, dedicated air handler units or local capture / containment devices.

iv. Options regarding central dust collection versus local collection processes, by which to isolate contaminants.

v. Special architectural features or layout to provide protection in lieu of HVAC solutions.

vi. Suitability of cooling, heating, dehumidification and humidification systems, by which to satisfy indoor design conditions during extreme variations in outdoors conditions;

vii. Maintenance problems if, for instance, exhaust air energy recovery systems are conveying hazardous materials.

viii. Factors affecting reliability, such as uptime, availability, quality system, installed redundancy, resource sharing between systems and by-passes for out of service components.

ix. Facility life expectancy and future flexibility: HVAC system components sized for future needs but currently operating at reduced capacity, may be incapable of providing adequate temperature or humidity control at reduced load.

x. Electricity outage and resulting recovery from interrupted operations can incur additional costs. Consideration of back-up generators can be beneficial in events of power failures.

xi. The cost of installing systems, with the associated training, together with continuous training due to staff turnover, can significantly escalate the cost component(s) for the smaller facility. Cleaning and maintenance of HVAC has to involve scheduling and coordination of maintenance activities. Poor maintenance practices may result in contamination of product.

3.2.6 Commissioning and Qualification

The process of commissioning incorporates a systematic method of testing and documenting of systems and equipment at the conclusion of project construction, but prior to validation.

Each component of the facility must be built in accordance with the plans and specifications and must be inspected, tested and documented by competent individuals. The purpose of creating and executing commissioning documents is not only for ensuring regulatory compliance; nevertheless, a well-documented

commissioning plan can become an integral part of validation. The validation perspective may help to distinguish the critical from the non-critical systems, equipment, materials or devices (ISPE, 1996).

3.2.7 Good Engineering Practice (GEP)

The ISPE guides have placed much emphasis on good facility design practice by engaging extensively in good engineering practice. Capturing the design evolution process in both new and renovated facilities is a critical requirement in good engineering practice (ISPE, 1996). In some way, all aspects of the facility must be documented by the engineers and construction personnel. Once this document has been approved by the "owner" or designers, it becomes the documentation plan, which can be referenced by validation protocols and can be assessed by regulators (Del Ciello, 2005).

3.3 Regulatory requirements for production of investigational drug product

The primary concern of this study is the establishment of a pilot facility for the manufacturing of Pheroid-based oral and topical products, which may be used in clinical trials and stability studies. The South African regulatory requirements for production of investigational medicinal products are such that they must be produced as per the SADOH (2005) guidelines on investigational medicines. These requirements are be governed by procedures which allow flexibility appropriate to the stage of development. Participant safety and consistent production of batches of the same quality would be better ensured by adherence to GMP guidelines (SADOH, 2005).

3.3.1 Pilot Production Facility

Although the South African medicines regulatory authority has not formally prescribed guidelines for 'pilot facilities', the requirements that have to be followed are the same as those for full-scale production facilities. This implies that any pilot facility would have to be registered as a manufacturer with the South African Pharmacy Council, according to Ms. M. de Beer (2006). The facility would therefore have to obtain a license to manufacture pharmaceuticals as per verbal confirmation with Mrs. S. Kahn (2006) from the South African department of health pharmaceutical policy and planning unit. To fulfil the requirement of full cGMP compliance will require regulatory inspection and approval of the facility. According to Mr. E. Motshitela (2006), the SAMRA inspectorate approves the license of a manufacturer if, upon inspection, it is satisfied that the facility is consistent with the regulatory requirements. The licensing

requirements in South Africa include the compilation of a site master file for the site as well as compliance with GMP.

3.3.2 Product development information

The International Conference of Harmonisation (ICH) Q10 on pharmaceutical quality systems states that: "Regulatory approaches for a specific product or manufacturing facility should be commensurate with the level of product and process understanding, the results of quality risk management and the effectiveness of the pharmaceutical quality system". Although regulatory authorities have made provision for various guidelines to assist manufacturers with achieving GMP compliance, it is an indisputable fact that quality production of the product is inevitably dependent on knowledge of the production process(es). The process(es) determine/s the conditions and control principles around which the product has been developed.

Establishing consistent and minimum parameters for facility design, as it is based on process and GMP requirements, include detailed knowledge of the following concepts:

3.3.2.1 Critical parameter/s involved

These are processing parameters (e.g. maximum heating temperature) that affect product quality, efficacy and / or stability. Manufacturers need to identify the critical parameters, based on knowledge of the process, and then document the rationale for later examination. The parameters required for the process affect the facility design and layout. They define the choice of equipment and, where necessary, also the architectural and material requirements that will ensure optimum product quality (SADOH, 2005).

3.3.2.2 Level of product protection

The risk of product contamination has to be evaluated and suitable preventative methods, that reduce this risk to an acceptably low level, should be identified and implemented. Often not all areas of an oral dosage facility require the same level of protection. Each area must be evaluated based upon its function, and which may vary at different times / stages and with different products. The protection requirement for a product may vary as it progresses through the manufacturing processes / stages to a finished dosage form (SADOH, 2005). The degree of contamination risk is based primarily upon the duration of exposure to the environment and the number of product changeovers within the facility. In general, the greater these factors, the greater the need for product protection by architecture or engineering systems (ISPE, 1996).

3.3.2.3 Product protection factors

Determining an appropriate level of protection for each area of the facility requires consideration of the following:

3.3.2.3.1 Product characteristics

Each product characteristic has to be reviewed and evaluated for its impact upon facility requirements. Product characteristics include toxicity or potency, physical properties such as density and physical state, hygroscopicity, ease of cleaning and light sensitivity.

3.3.2 3.2 Process considerations

i. receiving, storage and protection methods of materials;

ii. specific unit operations such as weighing, dispensing, blending / mixing, finished dosage and the arrangement thereof;

iii. material transport and handling; and

iv. methods for packaging and storage.

3.3.2.3.3 Degree of product exposure

i. Closed products or materials not exposed to the environment pose minimal risk of contamination, for example transferring a product in a closed system (e.g. pneumatic transfer, vacuum transfer or bin transport). Facility requirements such as architectural or HVAC needs may therefore be reduced.

ii. Open products or materials exposed to the environment therefore have potential for contamination either by or of the environment. This often dictates enhanced facility requirements such as airlocks or increased ventilation and filtering of air or heavy reliance on SOPs to reduce cross-contamination by operator tracking from one area to another.

iii. Intermittent exposure: Here exposure of the product or material is for a (very) brief period(s) during processing. It may be possible to implement a temporary protective measure(s) so that the operation may, in effect, be regarded as closed. This may be achieved by SOPs or local air flow control.

iv. High product / material potency or toxicity of necessity requires increased levels of protection for a given processing technique, primarily to protect the environment from the product (ISPE, 1996).

3.3.3 Facility flexibility

This concerns the number of different products that can be processed within a facility or a particular area of a facility. A facility could process:

i. a single product, which implies no flexibility, and foreign contamination would be the primary concern;

ii. multiple products in dedicated equipment, which implies moderate flexibility, and contamination between areas of the facility would be an additional concern; and

iii. multiple products in multi-purpose equipment, which implies high flexibility, and contamination within a process (equipment) and / or the individual processing area would be possible. In these areas the number and frequency of product changeovers and the type and frequency of cleaning procedures would directly affect the degree of contamination risk.

3.3.4 Required extent of validation

Systems are considered critical and need to be validated when they are either in direct physical contact with the drug product or if used to measure, monitor or record critical parameters. Support systems such as heat transfer systems, electric power and non-process water are necessary, but not considered critical, as they are not in contact with the product and do not need to be validated. The monitoring and control of critical parameters affected by these support systems, however, have to be validated. Any engineering system, equipment, piping, instrumentation, room environment, control settings or SOPs affecting critical parameters require strict control.

3.4 Conclusion

An investigation into factors of each of the areas relevant to the design of the pilot Pheroid production facility yielded a myriad of considerations that would have to incorporate into the design of an optimally operative Pheroid pilot plant. These include identification of the requirements for a GMP compliant facility and the requirements of the production process. The critical process parameters identified would subsequently guide the design of the facility and methods used to assure GMP.

The factors that influence the Pheroid-based pilot facility design at the North-West University include the following:

- Institutional (academic) challenges: Feasibility on campus, availability of facility, cost and staffing.
- Production process requirements: Enable the identification of critical parameters of the process, for instance temperature, humidity, airflow, likelihood of contamination, level of product of protection.
- Regulatory requirements: Provisions for manufacturing pilot production batches, licensing of a facility, achieving GMP and inclusion of various non-GMP considerations.
- Also included are non-GMP factors, such as engineering and architecture, that significantly contribute to the design and layout of air handling units, and electrical and utility components of the facility.

The above are generally relevant to pilot facility design at academic institutions and are addressed in greater detail in Chapter 4.

Chapter 4

RESULTS AND PROPOSED FINAL FACILITY DESIGN

4.1 Introduction and discussion of empirical findings

The empirical investigations conducted were to:

i. Determine the feasibility of establishing a Pheroid pilot facility at NWU, Potchefstroom campus;

ii. Gather knowledge of the Pheroid production flow processes and further establish what the critical process requirements are;

iii. Determine what structural components are needed for the premises based on the regulatory requirements;

iv. Determine what structural components are needed for premises based on the Pheroid process requirements;

v. Investigate the suitability of the allocated site as a Pheroid pilot facility based on the requirements.

The findings of these are tabulated in Annexure A. Due to the classified and proprietary nature of the Pheroid technology, precise or optimal process parameters will not be mentioned. These will be given in generic form to cover such parameters specifically relevant to the facility design. Data collection followed a qualitative approach. The selection of the data collecting tools varied based on the most suitable strategy for gathering the necessary information. These are described in Annexure A.

In this chapter, the initial theoretical model proposed was drafted based on the regulatory considerations, available budget and on the findings. The practical evaluation of the proposed theoretical model, followed by reworks on the model and two further evaluations (with their respective subsequent re-modelling) which would provide the basis of the final architectural design of the pilot facility are discussed in this chapter.

4.1.1 Discussion on feasibility findings

The findings in Table A.1 (Annexure A) provide positive evidence that the NWU as an institution can support the establishment of a pilot facility on campus. This support remains conditional to the priority of the safety of the students, the staff and the environment. These

could be easily ensured as the materials and processing involved poses little or no threat to the safety of the students. The Phertec R & D division (referred to as the "user" or "manufacturer" throughout this chapter) has placed conditions of controlled handling of certain active ingredients which may result in the development of drug resistance. Hence, the intent of the manufacturer is to contain and control the handling of these ingredients which further ensures the safety of the staff and students. This requirement would be considered throughout the design process of the facility.

The findings reveal that the NWU has adequate human resources, the necessary expertise, an available location for the facility and has the necessary instrumentation required for quality control.

The feedback in terms of the institutional requirements is positive. The limited budget and size of the site does however present challenges pertaining to process and GMP requirements. These factors, their relevant findings and their impact on facility feasibility are discussed below.

4.1.2 Discussion on process requirements

Process flow and critical process requirements of Pheroid and pro-Pheroid production are addressed in the discussion to follow. The necessary equipment required for the Pheroid and pro-Pheroid production are also discussed so that the layout, architectural, electrical and utility needs can be defined in terms of the process requirements.

4.1.2.1 Process flow and critical process requirements

While there are different types of Pheroid, as listed in chapter 2, the term "Pheroid" would be used as a collective term for all the types that are produced in a similar way, with the exception of the pro-Pheroid. Figure 4.1 provides an outline of the flow process in the manufacture of Pheroid. Figure 4.2 provides an outline of pro-Pheroid production.

The shaded areas of the Pheroid and pro-Pheroid production process are representative of critical process steps. These critical steps are dependant on certain conditions (temperature, pressure, duration, rate and sheer) which has to be accommodated for in the design of the facility.

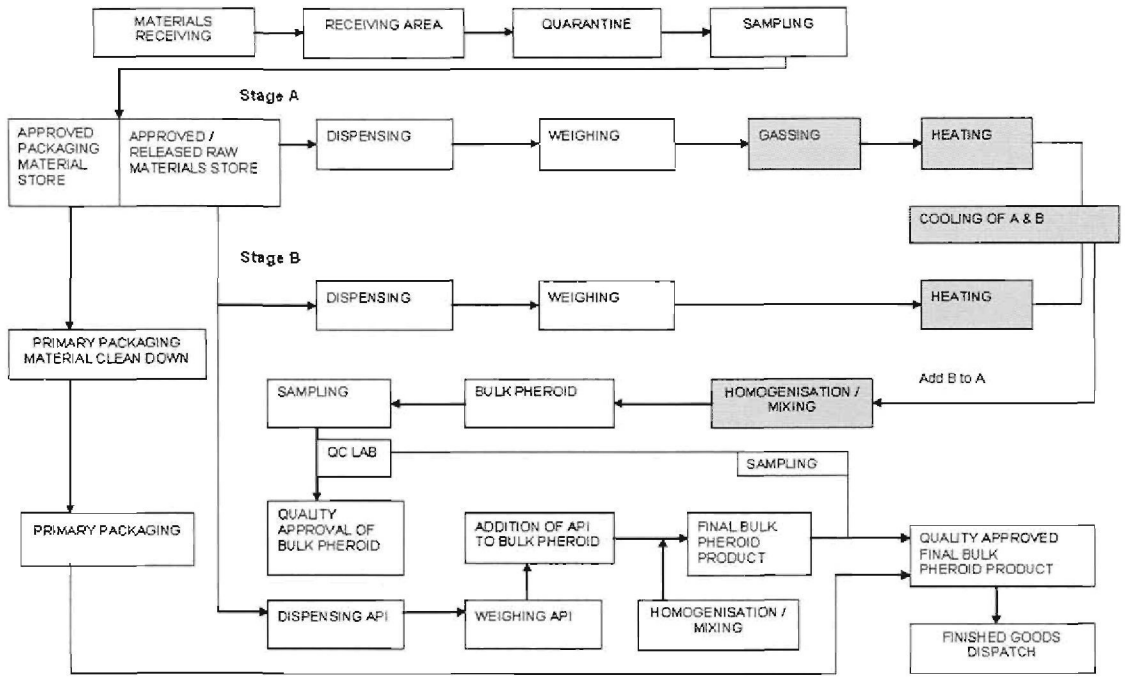


Figure 4.1 Process flow of Pheroid production.

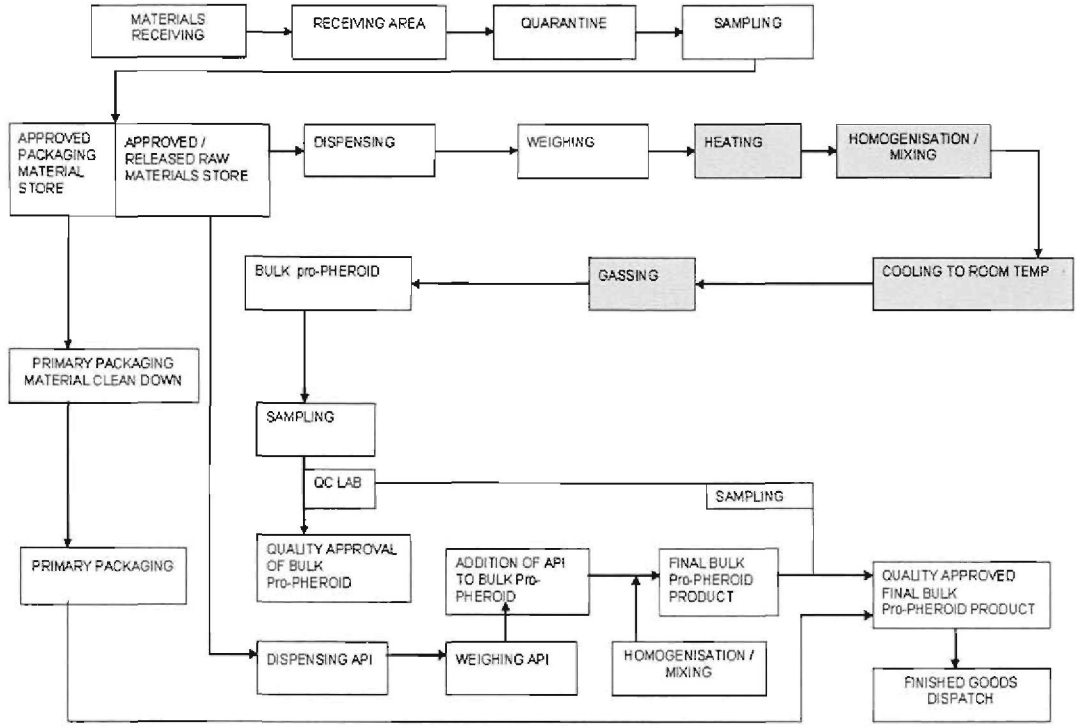


Figure 4.2 Process flow of pro-Pheroid production.

The critical processes are:

i. The gassing process requires that some of the pharmaceutical ingredients are gassed under pressure with nitrous oxide. This process occurs over a period of four days. About 80 to 100% of the total volume of the Pheroid / pro-Pheroid

account in order to provide adequate protection of product, personnel and materials. The flow of materials, personnel and product are important contributors to the layout of the facility. These factors provide information on the risk of contamination and cross contamination. A key architectural layout can be derived from material, personnel and product flow guidelines (ISPE, 1998., Jacobs, 2005 and Chu & Hofmeister, 2005). These necessitate the consideration of:

i. The logical, direct and sequential flow so as to minimise potential confusion, contamination and or cross contamination;

ii. Reduced distance that material has to move, which would minimise the risks of contamination and or cross contamination;

iii. Provision of protection against contamination. This can be achieved through the selection of suitable structural material in the design plan;

iv. The appropriate level of protection required within the facility based on process, product and regulatory requirements; and

v. Access to controlled areas.

Figure 4.3 reflects the flow of materials within a production facility. Figure 4.4 reflects the anticipated movement of personnel. These flow patterns are based on cGMP. The flow patterns of materials, personnel and product provide a genesis for the layout of the various facility component areas.

capacity of 10 kg or 10 litres. A larger vessel of at least 100 litres would be required for the production of pilot scale batches.

ii. Hot plate: In the experimental process, heating of the stage A ingredients in the Pheroid production process takes place with the use of a hot plate. The temperature is monitored with a thermometer. The heating of larger volumes of water in the pilot facility would require a larger source of direct heat. The heating of the larger batch sizes and the transfer of process materials from the heating surface to the mixing area within a confined space presents an occupational risk for worker safety. The identification and elimination of potential occupational hazard/s or risk/s, as defined by the Occupational Heath and Safety Act (OSH Act), are to be considered *a priori* (SADOL, 1993). This could be a negative contributor to the feasibility of a pilot facility.

iii. Microwave oven: The microwave oven used in the process raises the temperature of some of the process ingredients to about 130°C. The scale-up from experimental to pilot batch size would require an industrial size microwave oven. The size of this equipment which is estimated to take up a space of one cubic metre should be given consideration in the facility design process.

iv. Homogeniser: The homogeniser used for mixing would also have to be a larger type mixer which is able to achieve the same processing principles as the one used for experimental batch production. The larger mixer should also be accommodated in the design of the facility.

v. The weighing equipment: The experimental batch production process uses a balance. The pilot production facility would use scales that are larger and able to weigh the larger quantities as required by the process. The location of the balance in the weighing and or dispensing staging area would be considered in the design layout.

vi. Filling / Packing equipment: The manufacturer advised that a liquid filling machine would be procured for filling the oral liquid dosage form. The type has not been specified, however it would be of small scale and would occupy an area of approximately one square metre.

4.1.3 Discussion on regulatory requirements of a production facility

The findings on the structural requirements of the facility reveal several GMP considerations as well as architectural and utility components that need to be taken into

produced is gassed. This implies that gassing under pressure would have to take place in a vessel which is large enough to accommodate a volume of approximately 100 litres. The size of the vessel and utilities for gas and pressure has to be taken into consideration in the design of the facility.

ii. The heating process refers to two different types of heating processes. One process requires direct heating and the other, microwave heating. These distinctive processes require different heating equipment and these are to be considered in the design. In stage A (Figure 4.1) the heating involves raising the temperature through direct heating to approximately 70-75°C. During this stage, the larger of the two volumes or masses of ingredients are heated. Stage B involves microwave heating (the duration varies according to quantities prepared) and requires cooling of ingredients to approximately 70°C before transferring into the vessel containing the final phase of in-process stage A.

iii. The homogenisation process in Pheroid production is considered a critical process step as the sheer, speed and duration of mixing are important factors in producing the different types of Pheroid (Chapter 2). The presence of a mixer or homogeniser that would accommodate this processing is discussed further in the equipment requirements of the facility.

iv. The addition of the active pharmaceutical ingredient (API) is dependant on the physico-chemical properties of the API. If the API is highly water soluble, the addition of this ingredient would take place just after gassing of the aqueous phase as indicated by the dotted lines in Figure 4.1. Should the API have low water solubility it would be added after the Pheroid formation. In the case of pro-Pheroid, the API would be added once the pro-Pheroid mixture has been tested for its ability to form Pheroid under the required pH and aqueous conditions as indicated in Figure 4.2. This process may vary based on the effect of the API on the pH of the final pro-Pheroid mixture. This process has not been included in Figure 4.2 as it is still being investigated.

4.1.2.2 Process equipment

Findings of the investigation on the experimental batch production process reveal that the equipment required for the production of Pheroid products are:

i. Pressure Vessel: The process of gassing takes place under pressure within a pressure vessel. The vessel used in experimental batch production has a holding

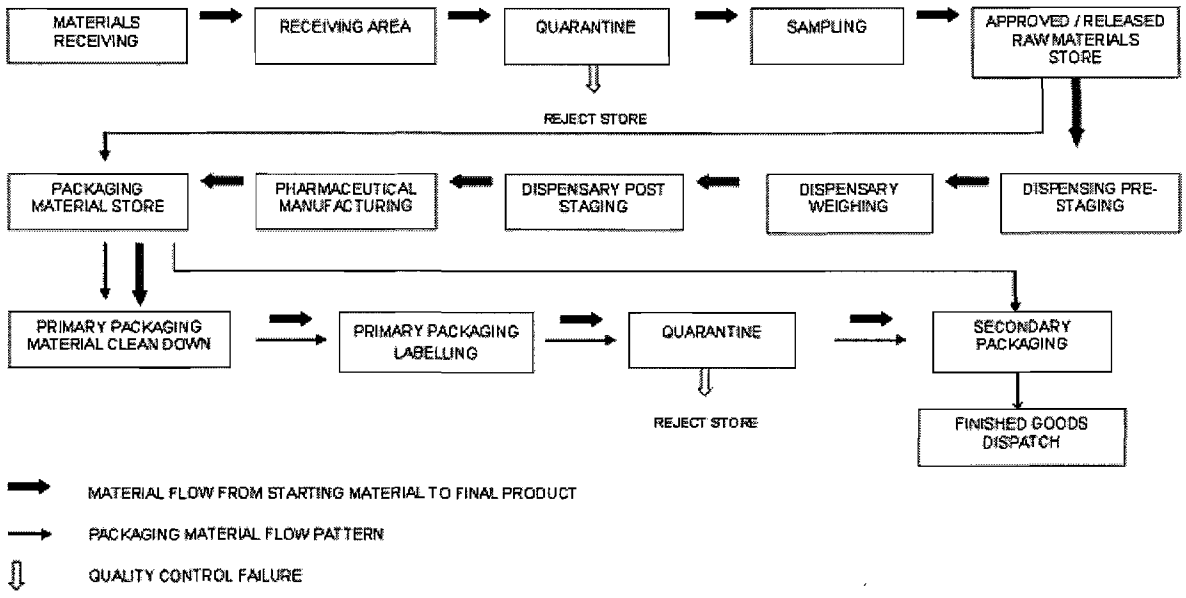


Figure 4.3 Material flow pattern.

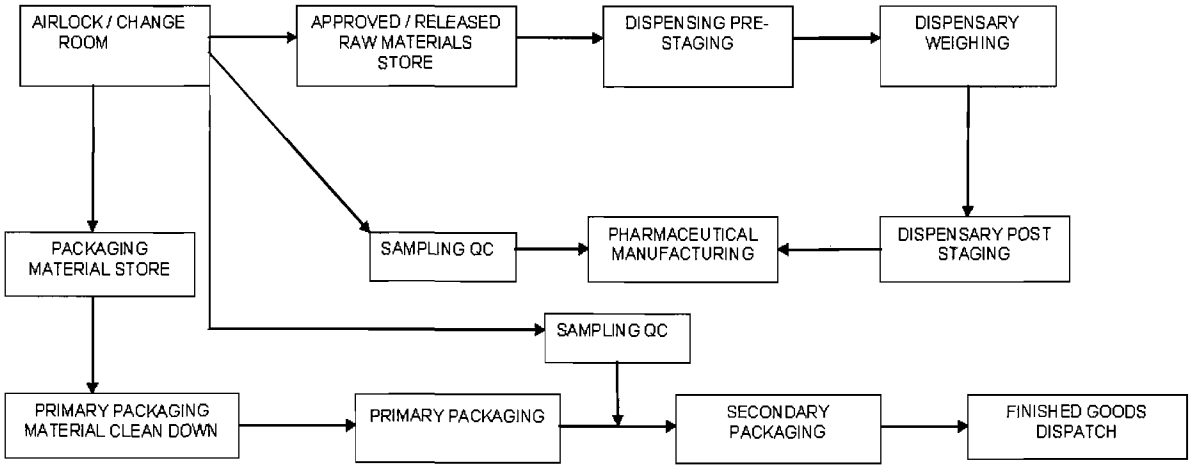


Figure 4.4 Personnel flow pattern.

The movement of materials, product and personnel provides an indication of the possible risk of contamination that would occur in a facility. The design of the facility should be such that the risk of contamination and cross contamination are minimised.

The facility should therefore have a quarantine area, an approved goods or released raw materials store, a dispensing area, a weighing area, pharmaceutical manufacturing area, packaging materials store, a packaging area, a goods rejected and goods returned store. The layout of these areas should be logical and sequential. The demarcation or separation of these areas reduces the risk of contamination. A box representation of the facility layout derived from these principle flow processes are reflected in Figure 4.5 (section 4.1.5).

4.1.3.1 Findings at the experimental laboratory

A record of findings at the experimental laboratory is given in Annexure A. Findings on procedures are recorded in Table A.3 (Annexure A). The findings reveal that whilst records in the form of experimental production batches, temperature logs and materials logs were kept, there were inadequate documentation in place that were able to define the relevant processes. The Pheroid and pro-Pheroid production was done on diarised requests and did not have a requisition for manufacture and hence traceability of these batches could not be verified. There were no defined areas of materials receipt, dispatch or transfer records. The findings in Table A.3 further emphasise the poor implementation of GMP and the need for suitable and adequate documentation in the form of procedures to govern operations and to ensure repeatability of the processes used. The available space in the experimental laboratory was insufficient to have defined areas of operations. The relevance of investigating the experimental laboratory was that it would provide an awareness of the current use of GMP in processing, materials, products and personnel flow, the equipment used and the likelihood of possible facility-related factors that would affect Pheroid processing on a pilot scale.

4.1.4 Discussion on findings of allocated site

4.1.4.1 Location and structural make up of premises

i. Location of the site: The allocated site is a laboratory of 7.55 m x 5.04 m in size. The laboratory was previously used for postgraduate research in pharmaceutics. The details of the precise location of the allocated site can be observed in the findings of the allocated site in Table A.8 (Annexure A). Figure A.4 is a floor plan of the location of the allocated site. This shows the location of the site relative to other offices and laboratories on that floor.

ii. Location of the site relative to the surrounding buildings: The site is located on the ground floor of the building occupied by the Department of Pharmaceutics. The building is located on the North-West University, Potchefstroom campus. This building is identified as building G2 on the campus map, Figure A.5 (Annexure A).

ii. Structural make up of the premises: Building G2, that houses room G20 (allocated site for the facility), is a four storey concrete, iron and brick structure. The internal layout and dimensions of the laboratory are reflected in Figure 4.6 (same as Figure A.6 in Annexure A). This figure has been repeated here for ease of reference.

iii. Detail of the structural make up of the interior of G20 is presented in Table A.8 (Annexure A). This detail covers the structural make up of the floor, walls, ceiling, windows, fixed furniture, electrical utilities, water supply, drainage and cleaning utilities, entrance and other attachments. These can be observed in the photographic detail of Figures A.7 to A.18 (Annexure A).

4.1.5 Discussion on suitability of the premises

The size of the facility, occupational safety and health, processing, cost and GMP requirements indicate that the allocated site would not be suitable as a pilot facility for the production of Pheroid based products. Elaboration of the effect of these factors is discussed below.

4.1.5.1 Factors adversely affecting the suitability of the premises

i. The risk of personnel being injured due to the heating and transfer of large volumes (approximately 80 litres) of materials would be considered an occupational hazard especially in the confined space of 7.55 m x 5.04 m.

ii. Worker comfort would be compromised when working with heat in a confined space. The temperature of the confined environment would be raised during the heating process thereby presenting a compromise on the immediate working environment.

iii. The process material, product and personnel flow, as per GMP requirements is represented in Figure 4.5. The solid lines represent the materials and personnel flow within the facility. The broken line indicates the movement of product and personnel out of the facility.

iv. The limited budget dictates that all existing utilities be maintained in their current positions. Hence, the cleaning area would inevitably remain where the water utility supplies are located on the existing site. The same applies to the electrical utilities with the exception of the lights. The weighing area will remain in the original location as indicated in Figure 4.6.

v. The specified user requirement that certain active pharmaceutical ingredients be contained so as to prevent the development of drug resistant organisms, does present a challenge. This is to be taken into consideration within the available space. This containment could be achieved with the use of barrier technology. Thus, an isolation area that will facilitate the contained weighing and mixing of the

relevant active pharmaceutical ingredients has to be included in the plan. The modified box layout and process flow including these changes is represented in Figure 4.7.

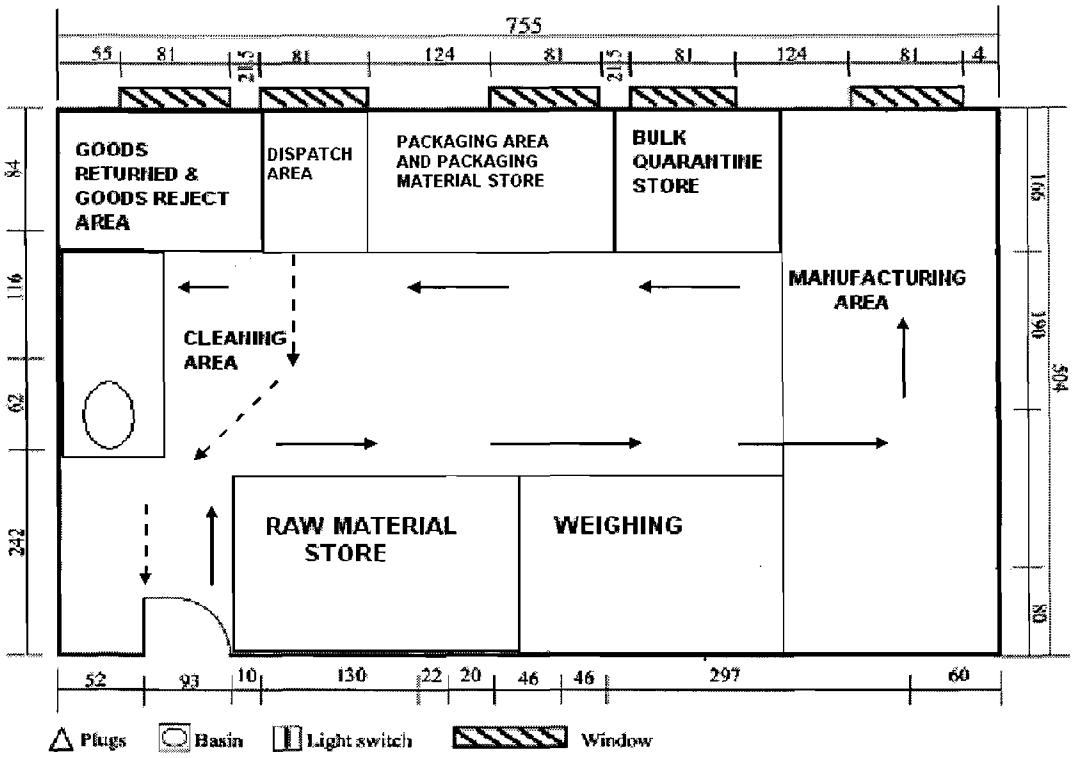


Figure 4.5 Box representation of facility layout and process flow as per GMP.

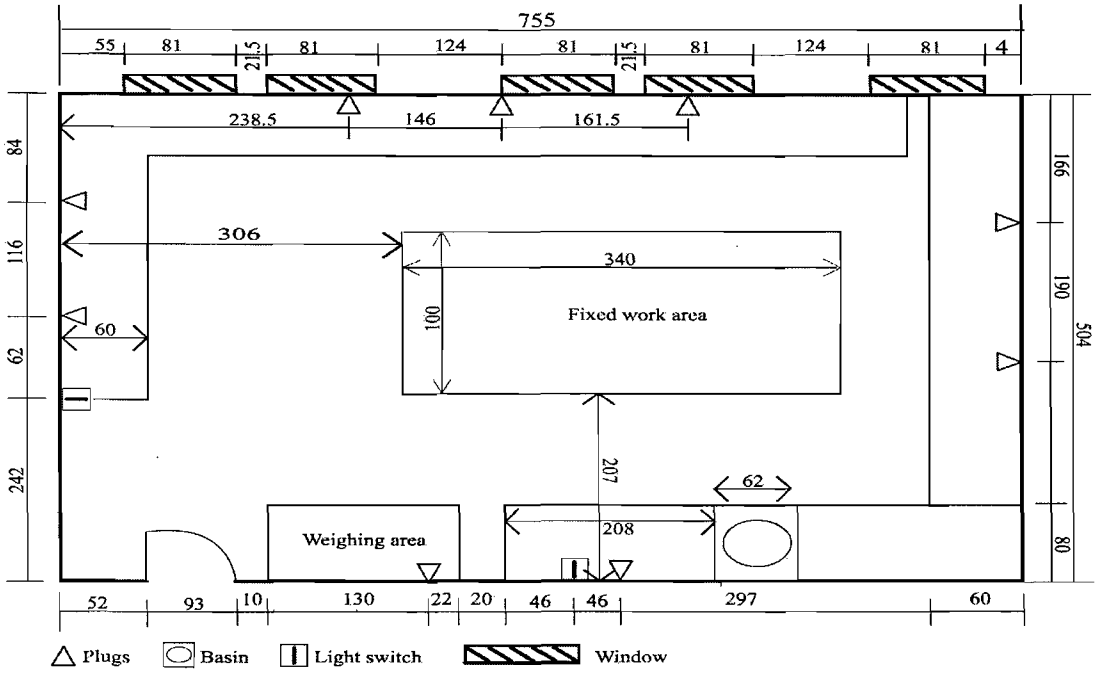


Figure 4.6 Original layout of the allocated site.

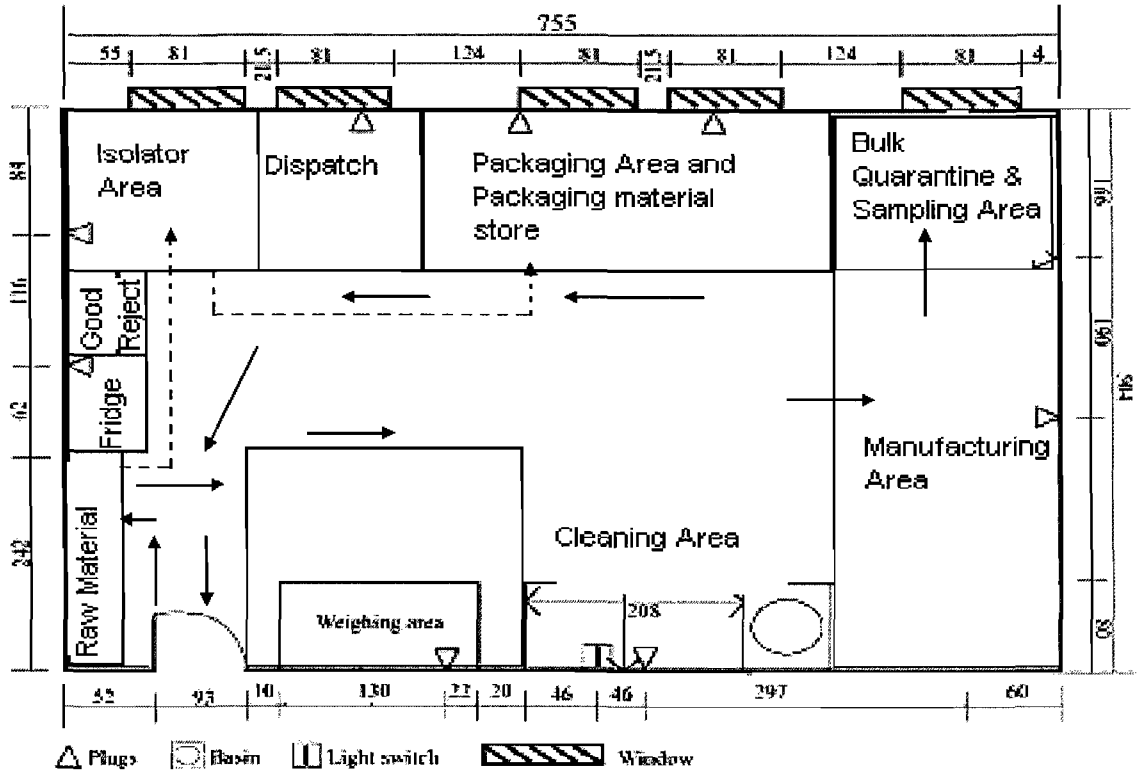


Figure 4.7 Box representation of layout and process flow for facility based on cost limitation.

vi. Raised ambient temperature due to processing implies that the stability of the raw materials in the raw material store would be compromised and resultantly affect the quality of the finished product. Thus, the raw material store cannot exist in this environment unless a change to the process heating is made, or a change to the way is found for the ambient air temperature to be maintained within acceptable limits.

vii. The Pheroid as a drug delivery system involves entrapping the active drug substance (Chapter 2). The Pheroid may also entrap particles (contaminants) present in the manufacturing environment. The findings from experimental batch production indicate that the process of heating, homogenisation and ultimately Pheroid formation takes place in an open manufacturing environment. The smaller surface area exposed to the environment with experimental batches has not shown significant deviations with trial batch production, the larger surface exposed and larger quantities of materials weighed in the facility may present with greater risks of contamination. This would increase the possibility of contaminants becoming entrapped in the product. This occurrence is a critical factor that would impact on Pheroid quality. Therefore, a method of ensuring limitation of possible

contaminants or providing a cleanroom manufacturing environment would be necessary.

The abovementioned factors all contribute to ultimately render the allocated premises unsuitable for a pilot plant. Unsuitability is further compounded by a limited budget that precludes installation of air handling systems that would have reduced contamination and improved worker comfort.

4.1.5.2 Considerations that could positively influence the suitability of the allocated site

i. The concern of process heating that results in raised ambient temperature, compromised worker comfort and the risk of worker safety could be reduced or eliminated by accommodating the heating process within the same vessel in which the pressurised gassing would take place. This can be achieved if the vessel has a built-in heating jacket capable of the required temperature and heating rate. Insulation of the vessel to minimise heat loss to the environment would be a necessity. Eliminating separate heating equipment also saves space.

ii. The vessel can be designed to provide for containment and to act as a barrier to possible contamination. This would imply keeping the vessel covered, but it should have an opening large enough to allow the addition of process materials. Hence, the resultant exposure of the product in the vessel to the outer environment and contaminants would be reduced.

iii. The vessel should be made of material that would be resistant to corrosion, to prevent contamination arising from lack of integrity of the vessel.

iv. Including a mixer meeting process demands, within the vessel would occupy less space and would further reduce contamination by minimising exposure of the product (as opposed to the homogenisation done with an external mixer).

v. Further improvements in space saving and ergonomics can be achieved by equipping the vessel with a clean-in-place (CIP) system, thereby negating the need to move it to a cleaning area large enough to accommodate it.

vi. A vessel of this size should be mobile to facilitate mixing in the isolation area with ease.

vii. The cost of a vessel, incorporating all these elements, will be high. However, the acquisition of a large pressure vessel plus a direct heating surface and a mixer

would also be expensive and must be weighed against the total cost and benefit of a specialised vessel of this nature.

viii. Another factor that would enhance the suitability of the premises would be the use of a HEPA filter air handling unit in the isolation area. Active ingredients that are weighed and mixed within the isolation area would not get channelled to the outer environment.

ix. The in-process and final product quality control would take place at a separate location as per GMP.

While the flow processes, as outlined in Figure 4.7, indicate a breakdown in GMP compliance, this can be remedied using suitable SOPs to address shortcomings. The user's policy of campaign batch production of one batch a week has the advantage of eliminating product mix-ups and reducing the risk of possible cross contamination. The use of a specialised pressure vessel, that would house most of the Pheroid production equipment, appears to be the only viable solution to the inadequacy of the premises. Although the specialised vessel is recommended, it would be necessary to validate that the Pheroid and pro-Pheroid it produced is of the same quality as the products obtained with the current experimental process.

4.1.5.3 Pheroid pressure vessel

The user / manufacturer requested that the facility design process continue on the premise that a specialised vessel, as described in the previous section, would be procured. The term Pheroid pressure vessel (PPV) would be used when referring to this specialised vessel. As GMP of the facility also includes process equipment within the facility (Chapter 3), it is necessary to ensure that the PPV meets the relevant Pheroid process requirements as well as regulatory requirements. Hence, the facility design would continue based on the following assumptions:

i. That the PPV will accommodate the following critical Pheroid production processes: a) gassing of relevant ingredients; b) heating of ingredients to the required temperature, c) homogenising or mixing at specified sheer, for a set duration.

ii. That the PPV is insulated to limit heat convection to the production environment.

iii. That the PPV has a suitable closure / lid that would enable addition of ingredients with minimal risk of product exposure.

iv. The PPV be constructed of material that is durable and resists corrosion.

v. That the PPV has a clean-in-place (CIP) mechanism.

vi. That the PPV would be easy to move around on an epoxy-surfaced floor, preferably having its own wheels that will not damage the floor surface.

vii. That the diameter of the PPV not exceed 1.3 metres and that the facility design would provide for installation of such a vessel with an entrance of approximately 1.5 metres wide.

viii. That the PPV does not have any protrusions that may extend the size of the vessel to greater than 1.5 metres.

ix. That the PPV has the necessary gauges for monitoring pressure and temperature, as well as gas regulators as prescribed by the SADOL (1996) "vessels under pressure regulations".

x. That the utility requirements for gas, water and electricity are supplied and accommodated in the facility plan.

xi. That the PPV would be designed, manufactured, registered, inspected and certified as per the SADOL (1996) regulations for vessels under pressure.

xii. That the PPV would be installed by the contractor / engineer of the PPV. The contractor would also do the installation and operational validation of the equipment.

xiii. That training on operation and maintenance of the PPV will be provided at installation by the commissioners of the equipment.

xiv. That the contractor will provide a cleaning validation on the CIP system of the PPV.

xv. That critical automatic safety shut-off or warning systems are present. Processes such as gassing under pressure do not require simultaneous heating. The process requirements are such that when the ingredients are heated, it would not be done under pressure. Therefore, a safety mechanism is needed which would automatically ensure that no heating can occur whilst gassing under pressure.

4.2 Presentation of a Theoretical Design

4.2.1 Rationale used for the theoretical design

Del Ciello (2005) propose that the layout of the facility, or the components to be considered for a conceptual design is essentially based on the process operational flow of materials, personnel and product, as indicated in Figures 4.1 and 4.2. These figures were however based on the process flow prior to the use of the PPV for other critical process requirements apart from gassing under pressure. Process flow incorporating the specialised PPV, which contains several of the critical process steps, is illustrated in the following process flow diagrams: Figure 4.8 shows the process flow of Pheroid production with the specialised PPV, and Figure 4.9 gives the process flow of pro-Pheroid production with the specialised PPV.

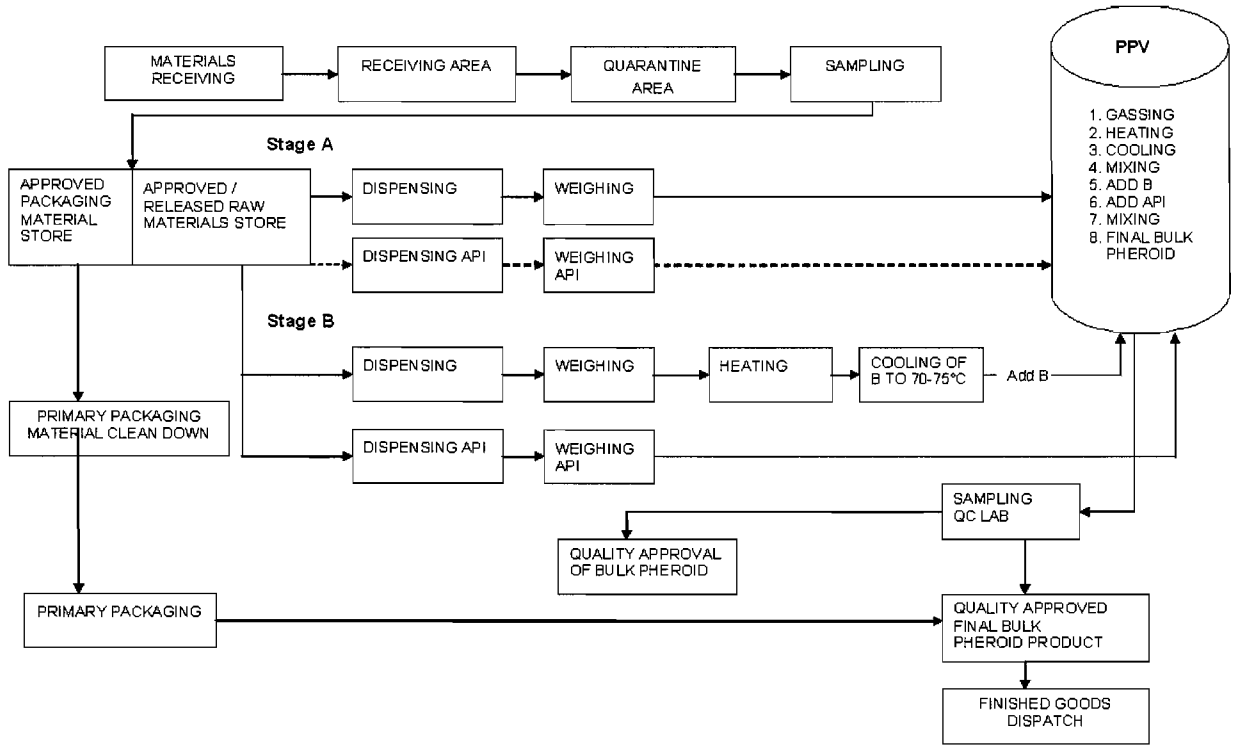


Figure 4.8 Pheroid production flow process with PPV.

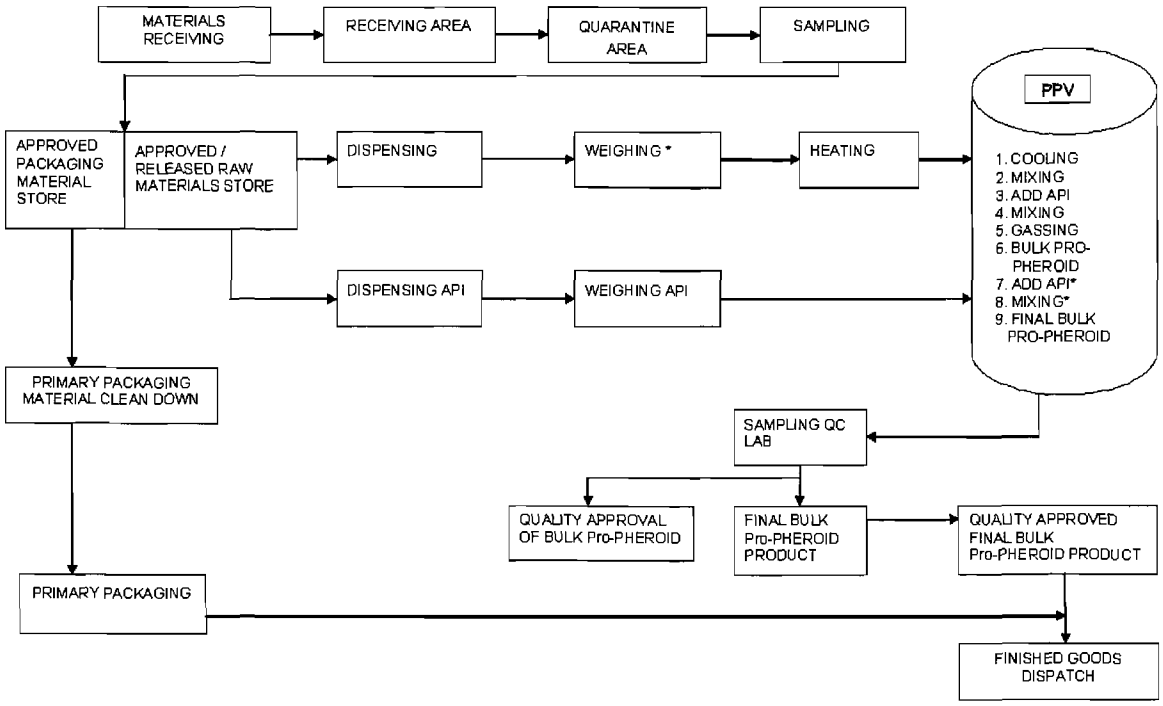


Figure 4.9 Pro-Pheroid production flow process with PPV.

Incorporation of the PPV has reduced the space requirements and allows for central placement of the utility supply ports (gas, water and electricity) for the vessel. Containment of various of essential critical processes reduces the risk of product contamination and makes it possible to house the PPV in an area that is practical for accessing necessary utilities.

4.2.1.1 The effect of PPV on the flow process

The PPV will be a multi-purpose unit, not only used to produce Pheroid product, but also important for limiting product contamination during processing. It will be the heating device, whilst also reducing heat convection to the environment, thereby minimising increases to the ambient temperature that could impact on worker comfort and the storage conditions of materials stored within the facility. It will reduce movement of staff, materials and products in the facility, thereby limiting the risk of contamination. The use of the PPV would lower in-process product exposure times which would reduce contamination.

4.2.1.2 Application of process requirements to conceptual facility design

It is not necessary to address each GMP issue with several design mechanisms or solely with facility design - standard operating procedures (SOPs) may be used to achieve GMP compliance (SADOH, 2005). Therefore, the same level of protection can be achieved whilst dramatically reducing costs.

One-way personnel flow, airlocks, special gowning and cleaning procedures to prevent contamination are generally not required for liquid dosage form production (ISPE, 1998). This is obviously dependant on the process requirements and the possible risk of product contamination and cross contamination. The manufacturer should apply one, several or all of these, based upon assessment of the contamination risk, to achieve the necessary protection and compliance.

The ISPE baseline guide for solid oral dosage form facilities was consulted and the requirements extrapolated for use in liquid oral dosage form facilities, because specific guidelines for oral liquid facilities are not yet available. Requirements for oral solid dosage forms are much more stringent than those for topical and oral liquid dosage form manufacture.

4.2.1.3 Alternative and non-GMP technologies

Some facility design requirements arise from decisions made to address non-GMP issues or preferences of the manufacturer, such as operator safety or strategic operating decisions. These non-GMP driven factors often affect facility design features aimed at achieving GMP compliance. The use of various non-GMP technologies may influence the cost of the facility. The user's prerequisite for the containment of active pharmaceutical ingredients can be achieved through non-GMP technology such as an air handling unit.

4.2.1.4 Risk of contamination

The risk of contamination, and the level of protection required, are based on:

- The duration of product exposure - the use of the PPV in the production process will decrease product exposure time.
- The frequency of changeover is reduced - the campaign production of Pheroid and pro-Pheroid reduces the risk of batch cross contamination that could arise with simultaneous and more frequent production of multiple product batches.
- The characteristics of the products - Pheroid's characteristic ability to entrap particles, places it at risk of being compromised in terms of quality should entrapment of contaminant particles occur.

4.2.1.5 Operating ranges

Acceptable operating ranges are based on product acceptance criteria. Engineering designers use the equipment design ranges to determine the design conditions. For example a blending / mixing room may have a design range of 30% to 50% RH (relative humidity), but the product in that room may be unaffected by humidity in the range of 20 to 70%. Therefore, the acceptable operating range for the room would be 20 to 70%. The operating range of the PPV is unknown, however the product which is Pheroid-based may not necessarily be affected by the humidity as it has an aqueous component. The pro-Pheroid may require more rigid humidity controls to prevent Pheroid formation. The PPV should facilitate shorter exposure times and hence lower incidence of unwanted events. The humidity operating range for the raw material store has to be low to protect moisture sensitive raw materials.

For each of the various component areas, as well as their equipment, acceptable operating ranges have to be decided upon for the following variables: temperature; humidity; air pressure; airflow; air change and lighting.

4.2.1.6 Good engineering practice

Good engineering practice recognises that all systems in a facility, whether process equipment, safety valves or rest rooms, routinely undergo some form of commissioning and maintenance. Good engineering practice capitalises upon the manufacturer's involvement with all stakeholders (engineers, managers, operators, quality assurance experts and others) very early in the design process to ensure that construction and commissioning of systems are documented correctly. In the development of the theoretical design, engineers were not consulted, as the ISPE and South African GMP guide were used to produce a theoretical model. The engineers were involved at a later stage to evaluate the theoretical model against practical aspects of engineering (Chapter 4 paragraph 4.3).

4.2.1.7 Enhanced documentation

Documentation would be required for critical systems and instruments. This adds two dimensions to quality i.e. change control and validation. Qualification or validation would be expected for critical systems to demonstrate consistent and correct operation. It would be essential that all testing follow approved protocols, the results of which must be recorded in a clear and consistent manner. The proposed design makes reference to the relevant documentation to ensure product quality.

4.2.2 Process requirements: Pheroid preparation process

4.2.2.1 Critical parameters

i. Gassing with nitrous oxide at the pre-determined pressure for a specific duration to achieve saturation (details of this process are classified). The quality and stability of Pheroid formed is dependant on this process.

ii. Heating of the oil phase to a maximum temperature of 130°C - if temperatures exceed this critical temperature, product quality is compromised.

iii. Heating of the water phase to approximately 70-75°C is critical in facilitating mixing.

4.2.2.2 Critical instruments and systems

Thermometers and pressure gauges are the only instruments used during manufacture, but other instruments are used to test for Pheroid formation, as well as the quality of Pheroid produced.

The zeta potentiometer is located in a laboratory which is separate from the pilot facility and will therefore not be discussed in-depth. Testing of the products and materials used in the pilot facility will be done by the analytical laboratory. Determining Pheroid formation and Pheroid quality also involves the use of a confocal laser scanning microscope (CLSM) which is housed in a dedicated unit. Instrumentation and control are discussed further in paragraph 4.2.7.

Thermometers used to measure process temperatures, as well as the pressure valves' calibration and controls have to meet process requirements. An enhanced level of documentation, assuring installation and operating qualification, would be necessary. Various manual processes require appropriate standard operating procedures (SOPs) and operator training. Such training needs are to be documented and verified. The PPV will have the necessary temperature and pressure gauges to be used for monitoring process conditions.

4.2.2.3 Level of protection

After taking into consideration the risk of contamination, as well as the nature of the product (Pheroid), it was decided that level 2 protection would be needed.

Also refer to 4.2.1.4.

4.2.3 Product protection factors

4.2.3.1 Product characteristics

The properties of the active ingredient or product composition can provide challenges to the manufacturing operation and its ability to comply with GMP regulations. These characteristics are discussed below:

i. Toxicity / Potency: The anti-retroviral agents (stavudine; lamivudine and nevirapine) and the anti-tuberculosis agents (rifampicin and isoniazid) do not pose threats in terms of toxicity or potency but the presence of these in the environment may eventually cause bacterial or viral resistance. Hence, the need for protection to minimise the possibility of resistance arising. As these agents are in powdered form, it would be necessary to ensure a level 3 or 'controlled approach'. This can be achieved either through facility engineering, isolator technology, masking or HVAC technology. Due to the financial limitations, the proposed theoretical design will engage the use of isolator technology.

ii. Physical properties: The dry forms of the abovementioned actives present a challenge with respect to product contamination, especially in multi-product facilities. The liquid or free-flowing materials may be more easily contained.

iii. Hygroscopicity: Low humidity environments may be necessary for correct storage of these materials. This will not only affect the HVAC system but also the room finish. Processing is not affected by hygroscopicity, as the Pheroid base has an 80% aqueous component. Isolation from the outer environment, lower exposure time to moisture and the use of suitable containers with low moisture permeability are necessary.

iv. Cleanability / Solubility: The poor solubility of various oils affects facility design and equipment selection. Cleaning of equipment can be achieved using clean-in-place (CIP) technology which would ensure uniformity of cleaning systems and cycles.

v. Light Sensitivity: Rifampicin and isoniazid are light-sensitive and the handling of these API's should be such that there would be little or no exposure to light. This can be achieved through closed processes or equipment designed to avoid light exposure during manufacturing. Amber glass can also be useful in minimising exposure to light.

vi. Sensitisation: There are no known cases of sensitisation with continued exposure to any of the above ingredients.

4.2.3.2 Process considerations

Specific API's (those prone to the development of organism resistance) have been classified to be handled in a level 3 protection area. This can be achieved by installing a HVAC system and / or isolator / barrier technology. Given the size of the pilot plant, it may be more cost effective to include an isolation area in which the relevant substances can be handled and manufactured. The isolator unit should have an air extraction system fitted with a HEPA filter (99,99%) to ensure that the particles drawn out of the unit are trapped, to reduce the risk of release into the environment.

For most products, Pheroid preparation would be followed by the entrapment of actives to yield the final bulk product. In cases where actives are highly water soluble, they may be added prior to the formulation of the Pheroid. In the case of pro-Pheroid, the actives are added as Pheroid formation would only take place upon ingestion. Only after quality approval will products be transferred for filling and packing.

Process considerations for the theoretical design include the following:

4.2.3.2.1 Materials receipt, storage and protection methods

The findings regarding the handling of raw materials indicate a lack of adequate control with respect to having a dedicated goods receiving area and recording of the 'quarantine' status of the materials until appropriate testing has been done to approve release. The design philosophy of the pilot facility has to ensure that the respective areas are dedicated for these purposes. Planning an area for raw material storage involves correct selection of location, architectural finishes and proper directional airflow to and from the raw material receiving and release stores. Each of these component requirements are considered as follows:

i. Raw material receiving store / area: In this area, raw materials are to be received and sampled. The location of this store should be such that it does not introduce contaminants to the processing areas or other raw materials. The raw material store should be a dedicated site for the handling of raw materials. This activity should be governed by an SOP for raw material receiving. Status labels indicating 'quarantined' should be applied to all raw materials received, until such time that the necessary quality tests have been performed.

ii. Raw material specifications have to be drawn up for each raw material received.

iii. Once raw materials comply with specifications, the quality control officer / manager may then assign a "goods approved" or "goods released" status.

iv. The areas for quarantined materials and approved materials should be separate from each other to avoid possible mix-ups during dispensing. In cases where this is not possible, for example with refrigerated items, it would be critical that the relevant containers be clearly marked with appropriate status labels.

v. The necessary SOPs and procedures, for the process of releasing of raw materials, have to be established.

vi. The prescribed storage conditions for raw materials received should be taken into consideration. A refrigerator may be necessary if storage requirements of any raw materials warrant it.

The proposed raw material store (Figure 4.11) will be a lockable cupboard. The cupboard has to be level with the floor surface for stability and should be no higher than approximately 2.0 m. The cupboard should have two distinct sections (side by side) to allow for separation of quarantined and released materials. The location of the cupboard should be along the left wall, near the entrance. The cupboard should stand flush against the floor so that it does not create a space for dust / dirt accumulation. The location of the store was selected based on the fact that all goods are to be received in the goods receiving area (office G14).

The movement of material and personnel is limited (through campaign production and appropriate SOPs for materials transfer) to prevent introduction of contaminants into the processing areas. Facilities that have more space are able to demarcate an area for this purpose, or an entire warehouse. The number of raw materials that would be handled at the pilot facility comes to approximately 12 items and hence it is not necessary for a large raw material store.

Specific unit operations in Pheroid processing include weighing and dispensing, mixing or blending, possible milling, finished goods bulk and dispatch areas. The location and arrangement of these areas are to be consistent with material flow requirements for cGMP.

4.2.3.2.2 Weighing and dispensing operations

As discussed in Chapter 3, the use of isolators in the weighing / dispensing operation would reduce the likelihood of contamination and would present opportunities for savings in terms of cleanability, cross contamination, containment, room HVAC and architectural finish. However, the trade-off would be specific attention, increased effort or costs that are likely in validation, equipment cost, throughput, changeover and space requirements.

The weighing area represented in Figure 4.11 will be enclosed, preferably with glass, up to a height of 2.0 m (not all the way to the ceiling). The enclosed space will provide containment, reduced turbulence and hence minimal disturbances which could result in inaccurate weighing. The location was chosen to make use of an existing weighing surface in order to save money through reduced architectural manipulation.

4.2.3.2.3 Mixing and blending process

The equipment (experimental batch manufacturing equipment) and process currently used, have introduced the possibility of contamination due to various stages of exposure. The size allocated for facility design cannot accommodate current processes, because cramped conditions will make the risk of contamination unacceptably high. This risk can be reduced by using closed vessels during processing. Scaling up the process introduces a further prerequisite – the equipment and pressure vessel need to be large enough to contain the larger batch sizes. Larger equipment would, in turn, require more space. The use of the PPV, designed to meet the process requirements and reduce the demands on processing space, was recommended in paragraph 4.1.5.3 as a pre-requisite for continuation of the facility design.

A Sylverson mixer has been chosen to be used for mixing (in the unlikely event of a mixer not being included in the PPV design). A mixing area, represented in Figure 4.11, has been allocated in the event that the process stays unchanged from current experimental batch production. The chosen location of the mixing area was selected based on process flow, allowing for convenient transfer of raw materials to the mixing area. There are no specific requirements except that the equipment installed would have relevant documentation (operational validation) and SOPs.

4.2.3.2.4 Milling

The manufacturer indicates that the raw materials received are to have the required particle sizes for processing, with the exception of rifampicin. Provision for milling will be made within the isolation unit to ensure containment of particulates.

4.2.3.2.5 Finished product and handling

The entire process, from dispensing to final product, should be adequately documented and controlled with the relevant "batch manufacturing documentation". Batch manufacturing documents are currently kept for experimental batches. The manufacturer has to now establish batch manufacturing documentation for pilot scale batches. The processes may vary slightly due to the size of the allocated area for the pilot facility. It is envisaged that adaptation of the equipment (PPV) to meet the process demands would provide an equivalent alternative to the current process. The PPV requirements have been discussed in paragraph 4.1.5.3.

Prior to filling, the final bulk product mixture would be sampled. It would then be kept in the 'bulk storage area'. The status of the product would be 'quarantined' until the results of quality tests, performed on a sample, are approved. The process requires that testing of Pheroid formation be done for both the bulk mixture (as for the in-process tests) as well as in the final product. Each of these testing processes should be governed by the relevant documentation, including specifications and the release criteria of the tests.

From a facility design perspective, an area should be dedicated for the holding or storage of final bulk product until release. The waiting period may expose the product to possible contamination. Containment through adequate closure systems should be sufficient to prevent contamination. Release documentation and SOPs would achieve control over the movement and the status of the final bulk product.

A final bulk product storage area has been included in the proposed facility design (Figure 4.11). The area allocated will be sufficient to accommodate a PPV or mixing drum (stainless steel drum of approximately 150 L). The available space will be sufficient for the purposes of sampling and storage. A physical barrier need not separate the area as the entire facility (with exception of the isolation area) would be handled as a level 2 protection area. A painted line on the floor surface to indicate the division would suffice, provided that the bulk product has been adequately labelled to indicate status.

4.2.3.2.6 Filling / Packaging

Once the product has been approved, it would be released for filling and packaging. These processes will take place within a dedicated area of the facility.

Documentation for filling and packaging will cover:

i. Bulk product transfer after status has been approved;

ii. Dispatch of bottles / jars and caps[1]; and

iii. Necessary labels[2] for the filling / packaging area.

When the equipment is cleaned, a status label should be applied, indicating the following: date cleaned; signature of the responsible person; and also the batch and description of the last product filled / packed. The process generally involves calibrating the oral liquid filler machine[3].

Once filling and closure of the bottles is complete, the product should be labelled (refer to SOP for labelling investigational product) with batch number and proposed expiry date clearly shown. Counting and reconciliation of printed and unprinted packaging material, as well as bulk product would then follow. The percentage yield of the process is calculated as per the batch manufacturing documentation. The final product in final packaging should be sampled again and tested prior to release. The goods are re-labelled to indicate their new status and are then allowed to leave the storage area on batch release (SOPs and documentation regarding final product release has to be established).

As the facility will be tasked primarily with the production of trial products, the specific labelling requirements will be varied and procedures to control labelling are designed to meet with specific protocol requirements of the trial products (SADOH, 2005). As the pilot facility will produce investigational drug products, it would be necessary to have tracing records of dispatch to various investigators. Blinding and other protocol requirements are to be executed by the responsible pharmacist in accordance to Good Clinical Practice (GCP). This would not be discussed further as the processes of packing labelling, distribution and transportation will vary and be designed to be protocol specific.

The design of the facility will include a filling and packaging area (Figure 4.11). The area will be closed off from the other areas within the facility. The enclosed area would be to minimise the risk of possible contamination. The preferred closure would be glass as it allows for the process and operators to be observed from outside. Glass is also easy to clean. The closure should reach from the ground to approximately 2.0 metres high, leaving the top open. This allows sufficient ventilation for worker comfort.

The ideal set-up for the filling and packaging area would have been a closed unit with filtered ventilation. This was not recommended due to space and budget limitations.

[1] Dispatch of bottles / jars and caps: The receipt and handling of packaging units should follow a defined procedure. Approved vendors of packaging components are documented.

Minimum specifications for the individual packaging components should be established. SOPs, for the ordering and receipt of packaging components, are to be established. Upon receipt, packaging material is status quarantined, sampled and tested. Once approved, it will be released to the goods approved / released packaging materials store. The area allocated for the storage of unprinted packaging components should be access-controlled and should also limit possible contamination of components during storage.

[2] Labels or other printed packaging materials: SOPs, for the ordering and receipt of labels, should be established. Labels received should be quarantined, sampled and tested to ensure compliance with specifications. Once approved, a status label ("approved") should be attached to the package and the inventory of labels adjusted accordingly. A strict policy on requisition, dispatch and reconciliation of labels has to be implemented. Labels are generally locked away and access to the keys is limited to specific staff members, responsible for the dispatch of labels. A dedicated access-controlled area with proper storage conditions, to avoid damage, should be allocated.

Storage for printed and unprinted packaging material will be in lockable units / cupboards in the filling / packaging area. Having a lockable cupboard in the packaging area eliminates transportation from another storage area, decreasing the risk of mix-ups, misplacement and loss. Accountability of printed packaging components is critical in GMP. The lockable cupboard will provide the necessary access control.

[3] Oral liquid filler machine: This apparatus is still to be procured. The operation, calibration and controls should be adequately documented in SOPs. An area of one square metre was allocated for this apparatus, whilst the workspace beyond the equipment should be sufficient for operator handling and movement of the product.

4.2.3.2 Material transport, handling, packaging and storage

Material transport, handling, packaging and storage are controlled through process flow, design considerations and operating procedures. Processing from raw material to final product will take place within the pilot facility. The only materials transported are the samples (in various stages of processing) for quality testing purposes. The process of sampling and testing will be described in relevant SOPs. The packaging and storage of the final product has implications on facility design and architectural considerations. While the storage conditions for the product can be assured in dedicated storage spaces, the accessibility of product for dispatch should also be controlled. Final product control can be achieved with order and dispatch requests.

4.2.3.3 Process equipment requirements

4.2.3.3.1 Facility requirements for the PPV

As the batch sizes to be produced in the pilot facility would be about 100 L, the Pheroid processing site should be large enough to accommodate at least two 100 L mixing vessels. The one PPV dedicated to Pheroid production and the other to pro-Pheroid production. The processing area should have the necessary utility fittings for potable water, both for connection to the vessels and for cleaning of other mixing vessels. Obtaining large enough heating and cooling systems for the stage A (Figure 4.1) preparation would be adequately addressed by the PPV.

A description of the relevant criteria to be met by the PPV was provided in paragraph 4.1.5.3. The PPV has been the pre-requisite for the continuation of the pilot facility design, because it accommodates certain process requirements that would otherwise not be feasible within the allocated facility. The benefits of the PPV extend further to improving the process efficacy and reducing waste (energy and materials) due to reduced handling of materials.

Other benefits of the PPV:

i. Accommodation of process heating with reduced health and safety risk;

ii. Less heat-loss to the surroundings will make it possible to maintain temperatures in a range suitable for having the raw material store, filling area and bulk storage area within the same facility.

iii. Improves worker comfort in terms of temperature and humidity;

iv. Less handling of large volumes of heated mixtures; and

v. Reduces unnecessary handling of the gassed water.

Required features and fittings, needed for optimal functioning of the PPV, need to be identified so that they may be incorporated into the facility design. The following have been identified as possible requirements:

i. Fittings and controls to enable gassing under pressure. These should be able to accommodate pressures of up to 200 kPa;

ii. Electricity is needed to power the PPV's mixer (if included) and heating jacket. The electrical fittings need to withstand the current needed to heat an approximate volume of 100 litres of water to 80°C in less than an hour;

iii. The water supply port on the vessel should connect to the potable water supply utility within the facility. Drainage should be such that the heated water can be quickly drained to allow for timeous cooling of the mixture;

iv. The CIP mechanism will require supply of potable water and electricity - specialised connecters may be required;

v. The PPV's mixer must be able to maintain a speed of 13500 rpm for the required duration of mixing (duration dependant on the volume of product produced); and

vi. The PPV must be fitted with a product drainage port. A pneumatic system may be required for drainage of viscous products. The drainage port may have a connector that could be directly attached to the product filling machine.

At this stage of the facility design, the PPV design had not yet been finalised. Much planning and engineering would be needed before a proposed design could be drawn up for use in the facility design process. For purposes of plant design, knowledge of the required equipment and processes are critical in order to identify factors that need to be considered. For continuation of the facility design, a simple hypothetical diagram (Figure 4.10) of the proposed PPV was drafted based on the prescribed requirements. This was used to illustrate the process demands on the proposed PPV and the demands of the PPV on facility design. As the PPV would be indispensable to the functionality of the pilot plant (in the allocated space), provisions are to be made to accommodate the PPV in terms of space, utility requirements, movement and anticipated attachments necessary for the production process.

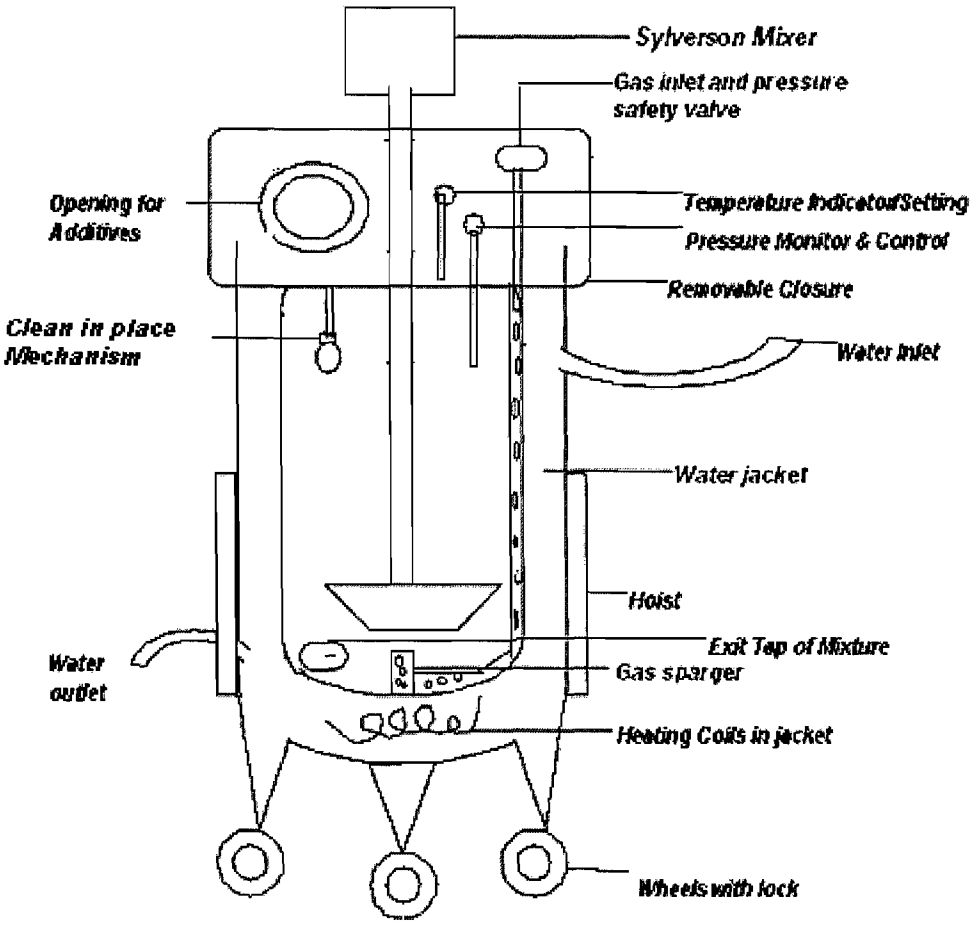


Figure 4.10 Pheroid Pressure Vessel (PPV).

The isolation unit of the facility should also have the necessary connections for supplying water and electricity to a PPV.

4.2.3.3.2 Other equipment used in processing

Whilst none of the following equipment has yet been acquired, estimates of capacities and equipment requirements are factored into the facility design.

i. Industrial microwave: The microwave should be able to accommodate 20 L of oil phase at a time. A space of approximately one cubic metre would be allocated. Electricity and lighting must be provided.

ii. Homogeniser / Sylverson mixer: It is planned that a mixer will be included in the PPV. Provision will however be made for an external mixer. Electricity and adequate space (one square metre) will be provided.

iii. Filling machine: Use of a bench-top liquid filling machine was proposed by the user. One square metre of surface area, and an electrical socket will be provided in the filling / packaging area.

iv. Gas cylinder housing and connectors for the supply of nitrous oxide to the PPV: Safety regulations suggest that gas cylinders should ideally be housed outside of the laboratories. Provision has however been made for gas cylinders to be housed in cupboards designed specifically for this purpose. Architectural changes to the existing facility that would have allowed for the gas supply to pass through the wall to the PPV, have been too expensive. Instead, a cupboard, capable of housing two gas cylinders, will be built near the PPV.

v. Weighing equipment: An industrial scale, as well as a sensitive laboratory balance (used for weighing small amounts of active substances) will be needed. Both require electricity and adequate lighting.

Required documentation for process equipment includes procedures for installation, operation and validation, as well as maintenance plans and cleaning protocols. The PPV would further require documentation confirming registration / certification (SADOL, 1996).

4.2.3.4 Proposed areas within the facility

4.2.3.4.1 Raw materials store

The raw material store will be a cupboard, 60 cm x 240 cm, with two doors dividing the unit horizontally. One part will be used as the raw materials quarantine store and the other as the raw materials approved / released store. Shelving within the cupboard must be able to accommodate at least 2 x 60 kg drums in each lower compartment, with smaller shelves higher up.

A thermometer must be placed in the raw material store and temperatures recorded on a daily basis. Stock control systems and procedures for receipt, sampling, release and dispensing will have to be set up to regulate the handling of raw materials. Status labelling is essential, especially for raw materials stored in the fridge.

4.2.3.4.2 Rejected goods store

This will be a cupboard or a single vertical standing unit / cabinet, 60 x 100 cm that will be lockable and hence access-controlled. Stock control will be achieved by SOPs and status labelling.

4.2.3.4.3 Isolated mixing area

This is a dedicated area (164 x 250 cm) area in which certain API's will be mixed. Isolation will minimise environmental and personnel exposure to the substances. Procedures for the use of this area, together with the prescribed 'batch manufacturing' requirements, will assist in ensuring control. The construction of this unit will require a level 3 approach and should include the following:

i. An air handling system with a HEPA (99,99%) filter;

ii. A ceiling constructed of gypsum board panels painted with epoxy;

iii. Joints between the wall and floor, and between the wall and ceiling should be rounded for easy cleaning and reduced potential for dust accumulation;

iv. The floor should be smooth cement with an epoxy seal;

v. The walls should be smooth and painted with epoxy resin;

vi. Light fittings should be recessed;

vii. Windows should be smooth, sealed and easy to clean.

The unit should be completely closed off from the rest of the manufacturing plant. The two sides without walls should be closed off with vinyl or glass panels. Using coloured glass can control the intensity of light entering the unit. Specific SOPs are to be established for the cleaning of this area.

4.2.3.4.4 Filling and packaging area

This area (356 cm x 188 cm) will be separated from other areas to avoid mix-ups. Enclosing this area will reduce the risk of contamination during filling. The type of materials used for closure is not critical, but should adequately distinguish the functions of this area from other areas. It is required that windows be sealed to reduce possible contamination during filling and packaging. Printed packaging materials, such as labels, will be stored in a separate cupboard. Unprinted packaging materials will be are kept in a secure, closed and clean unit. A lockable cupboard within the packaging unit would suffice. Procedures on regulating all processes associated with filling and packaging materials need to be established.

4.2.3.4.5 Final bulk product and sampling area

This 150 cm x 188 cm store should be separated from the mixing and filling area. Products have to be tested for compliance with prescribed specifications before being packed. Separation, labelling and suitable procedures would prevent errors of remixing / over-processing. Stored materials could be separated from the rest by markings on the floor and with appropriate status labels on the vessels. Windows should be kept closed when products are in this waiting area. A physical enclosure would further reduce risk of contamination and mix-ups. A procedure should be established to govern the process of sampling.

4.2.3.4.6 Pheroid production area

This area, 307 cm x 450 cm, will be open as it is assumed that much of the critical aspects of Pheroid processing will take place within the PPV. Experimental batches produced before, were always less than 10 L. In many instances the batches produced were as small as 100 g. Experimental production had been confined to glass beakers. The quick heating and cooling in the small containers had minimised product exposure time and hence limited contamination. If the same process were to be used for production of 100 L batches (pilot scale), whilst adhering to GMP guidelines, the current allocated production space would be inadequate.

The recommendation of containing the Pheroid production process in one vessel had been adopted as an integral component of the design of the pilot facility for Pheroid production. The allocated area would be able to house no more than two PPV vessels with an approximate diameter of 100 cm each. The relevant connectors for gas and water (supply and exit) will have to be located in this area. The electricity supply for the PPV, microwave and homogeniser will also have to be accommodated in this area. A sink, for washing utensils and a utensil storage area will be included as well. The area would further house at least two gas cylinders for the gassing process. Adjacent to this, in the open space, would be a mixing vessel. This is included in the design in the event that a mixer cannot be incorporated into the specialised PPV vessel. The process details are dependant on the final design of the PPV, the nature of the actives and the likely entrapment stability of the product. Batch manufacturing documents, that are product specific, would dictate the process. Special mixing, as defined for the isolated area, would be possible after Pheroid formation provided that the PPV is mobile so as to be transferred from the production area to the isolation area. The assumption that the PPV would have a CIP system does not imply that provision for a cleaning area, and the relevant cleaning procedures and status labelling, should not be anticipated.

4.2.3.4.7 PPV areas

This is an area, within the Pheroid production area, dedicated to housing the PPV and its necessary utilities. Whilst the PPV can be assumed to be a mobile unit, it is necessary to identify the areas in which it will be operating. These locations have been identified as: Pheroid production; isolation; final bulk sampling and possibly filling areas. The area in which all utilities for the PPV should be present is the Pheroid production area. The isolator area would require the electrical and water supply utility. Gassing will not take place in the isolation unit.

4.2.3.4.8 Weighing area

This area (200 cm x 170 cm) will be enclosed, especially when weighing small quantities, because turbulence can affect the accuracy of the balance. Enclosing this space will reduce possible contamination and will also protect balances from accidental interference and damage.

4.2.3.4.9 Other

The open area should be fitted with an air conditioner or suitable air supply to ensure adequate ventilation for worker comfort. A desk should be available for keeping records and documentation.

4.2.4 Process support and utility systems

The requirements for process support and utility systems are discussed in the following sections.

4.2.4.1 Process system

Water used in processing should be USP grade purified water. As the water will not be produced by the pilot facility, its production will not be discussed in the design of the facility. The USP grade process water will be supplied by an analytical laboratory on the NWU campus. It will therefore be considered a raw material that would undergo the same receiving process as any other raw material. A contract should exist, between the supplier and the manufacturer, covering the supply and specifications of the process water.

4.2.4.2 Process support system

The CIP system of the PPV could be considered as being process supportive. The heating / cooling jacket as a component of the PPV also has a supportive function. These support mechanisms will require validation.

Utilities include supply systems for air, potable water system and floor drainage. These systems are site systems that are generally not made specifically for the process. The location of the utility systems is critical with respect to the fitting requirements of the PPV. The potable water supply will also be used for cleaning. The drainage port of the PPV's water jacket should be on the ground and should be leak / spill proof. Drainage is often an area of concern, because water spillage as water spillage or accumulation in crevices would support microbial growth. The sink's drainage should also be located on the floor, within the sink unit.

It should be noted that, due to the budget constraints, many of the existing utilities and support utilities will be retained in their current locations. This is why some divisions of the facility are to be located in areas which are not necessarily compliant with the personnel, material and product flow principles. Many of these systems are to be supported by SOPs to ensure that product quality and integrity would not be compromised.

4.2.5 HVAC system

The use of specialised heating, ventilation and air conditioning (HVAC) systems is needed to ensure that process critical parameters and levels of protection are achieved. It was found that the cost of HVAC requirements for GMP compliance may be reduced with the concurrent use of other technologies such as isolator / barrier technologies or closed processing systems whilst, still achieving cGMP.

It has been established that certain critical parameters will be independent of room parameters. For instance, heating will be isolated within the PPV or microwave. Potential contamination by air-borne matter will be controlled by using a closed processing system such as the PPV.

It is clear that the processing requirements are not dependent on HVAC. However, non-GMP design considerations are to be taken into account where the windows are to be sealed off to reduce the possibility of environmental contaminants into the process, or where escape of the particulates from the facility to the external environment poses a threat. Possible movement of air from the entrance to the processing area will be a potential source of contamination. The rate of air entry can be reduced if the door is kept closed during manufacture. This does not pose any problems, especially in the first four days of the manufacturing process, as the process of gassing does not require staff to be present throughout. Alarms on the PPV and pressure regulator will serve as safety monitors during the process. After this stage, further processing will require the presence

of production and quality staff. Factors relating to ventilation are discussed in the following sections.

4.2.5.1 Worker comfort

Occupational health and safety regulations require a range of 25% to 60% RH for worker comfort where occupancy would be continuous. Also, adequate ventilation, with approximately 20% fresh air should, be supplied to the work environment in which occupation is continuous.

4.2.5.2 Air systems

Whilst processing does not demand varied humidity or steam systems, it is important to consider the effect of recirculation of unfiltered air from one process space to another. The facility does not have any air handling units, with the exception of the isolation unit, hence recirculation is excluded. As GMP guidelines don't stipulate the required number of air changes per hour to achieve desired levels of protection, an air change rate of between 4 and 20 per hour is recommended based on the air flow into and out of work spaces to ensure adequate ventilation for worker comfort. An air conditioner, capable of these air exchange rates is to be installed in the processing area. The direction of air flow should be from the processing area process towards the exit.

The isolation area will be fully enclosed and should be fitted with a suitable air supply system. A ventilation system providing an air exchange rate of between 4 and 20 would be required (ISPE, 1998). However, an air extractor with a particulate matter air filter (99,99%) should to also be installed. The filter will ensure that substances with controlled handling requirements are not allowed to escape to the outside environment.

4.2.6 Electrical considerations

Electrical systems in a liquid oral dosage form facility limit the amount of static charges due to higher humidity as opposed to amount of static occurring in solid dosage form facilities. Hence electrical system design, humidity control and equipment locations, to limit static generation and ensure equipment safety, would not be a critical concern in a liquid dosage form facility. The cleanability of electrical equipment, light fixtures and electrical devices however, are of primary concern for GMP compliance.

4.2.6.1 Wiring and lighting

Wiring should allow easy maintenance and accessibility to junction boxes. The recommendations for lighting and wiring for the facility are based on the findings and recommendations in literature.

The selection of sunken or recessed devices will limit accumulation of dirt and dust. The isolation area should have either gasketed or sealed light fixtures, or the fixture could be located outside the area allowing for light to pass through the glass barrier. Fixtures in the level 2 protection area should not be located directly above exposed products or materials so as to prevent accumulated dust from becoming dislodged and causing contamination. In a level 3 protection area, the fittings are to be arranged and designed to prevent any accumulation of dust and foreign materials. Flush mounted fixtures, recessed fluorescent fixtures or tear drop fixtures may be more appropriate. This has been applied in the design of the theoretical model.

The proposed design has included a minimum of nine (9) fluorescent sunken / flush ballasts. Refer to figure 4.12 for diagrammatic depiction of the location of lighting for the proposed theoretical design of the pilot facility. Light fixtures will be located:

i. One along the entrance of the plant;

ii. One in the weighing area just above the balance;

iii. One in the Pheroid formulation area, just above the microwave;

iv. One between the basin and gas cylinder housing;

v. One in mixing area;

vi. One in bulk sampling area;

vii. One in packaging area;

viii. One (in the isolated area must be flush against ceiling or) immediately outside the isolation area such that adequate light may pass into the unit. This light should have adjustable intensity settings to allow dimming when handling light sensitive anti-infective agents;

ix. One light fitting should be centrally located in the processing area.

4.2.7 Instrumentation and controls

The findings indicate the importance of instrumentation and controls, as well as the need for their validation when they are either in direct physical contact with the drug product or used to measure control or to record critical parameters. The instruments, used to establish whether Pheroid has formed or whether entrapment of active substance has taken place, are:

i. The confocal laser scanning microscope (CLSM)

ii. Malvern Mastersizer

These instruments are located in the quality control unit which is separate from the pilot facility. The testing of materials and products would be done by the quality control unit. The good laboratory practice (GLP) requirements for the above instrumentation are to be addressed by the analytical laboratory of the quality control unit. Both critical and non-critical device requirements are to be provided by the quality assurance unit of the pilot facility.

4.2.8 Other considerations

Many GMP compliance issues include factors that fall outside the scope of systems operations, but do however influence quality and productivity. Some issues are:

4.2.8.1 Personnel hygiene

The SAMRA application for licensing prescribes the completion of a site master file (SMF) wherein issues of personnel health and monitoring thereof are to be recorded. The necessary procedures for addressing personnel health and absenteeism are to be established and the delegation of responsibilities of key staff members is to be documented.

4.2.8.2 Rodent and pest control

Procedures are in place at the University, however there may be a need to modify the approach with regards to the production facility.

4.2.8.3 Safety and evacuation procedures

These are to be established in collaboration with the health and safety official of the pharmaceutics building in which the pilot facility will be located.

4.2.8.4 Noise consideration

Some equipment may generate noise. The impact of this is to be assessed. The campus environment may necessitate the use of silencers. The equipment is known to produce noise during mixing, however the exact noise levels still need to be measured. The environmental regulations for workplaces stipulate that personnel should not be exposed to noise levels equal to or greater than 85 dB (SADOL, 1987). The noise generation of the PPV is unknown.

4.2.8.5 Environmental consideration

Although the initial feasibility study did address possible environmental challenges, the environment is anticipated to be constantly changing and it will be necessary re-evaluate these considerations in time.

4.2.9 Diagrammatic representation of the proposed theoretical design (Model 1)

The initial draft design, called the theoretical model (also referred to as model 1 for ease of reference), was based on the findings of process requirements, GMP requirements (as per the South African GMP and WHO guidelines) and the available space and budget. A diagrammatic representation of the design is given in Figure 4.11.

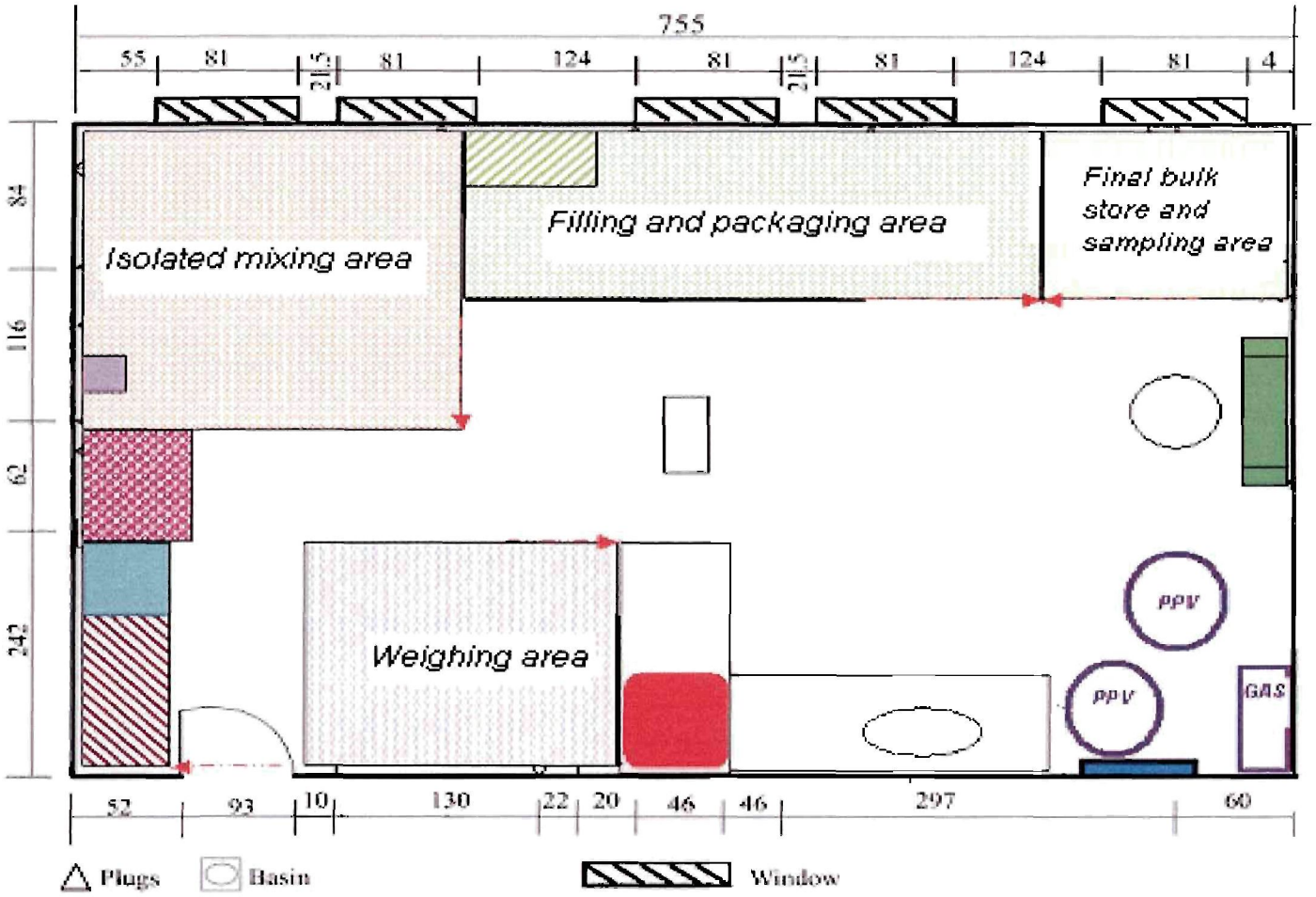


Figure 4.11 Theoretical design of the Pheroid facility (model 1).

Legend for Figure 4.11

	Closures with sliding doors
	Industrial microwave oven
	Panel of water supply connections to PPV
	Housing for gas cylinders (N_2O)
	Refrigerator
	Raw materials store
	Rejected goods store
	Weighing area
	Isolated mixing area
	Filling and packaging area
	Packing materials store (cupboard)
	Final bulk store and sampling for QC area
	Pheroid manufacturing area (open area)
	Work surface
	Mixing area

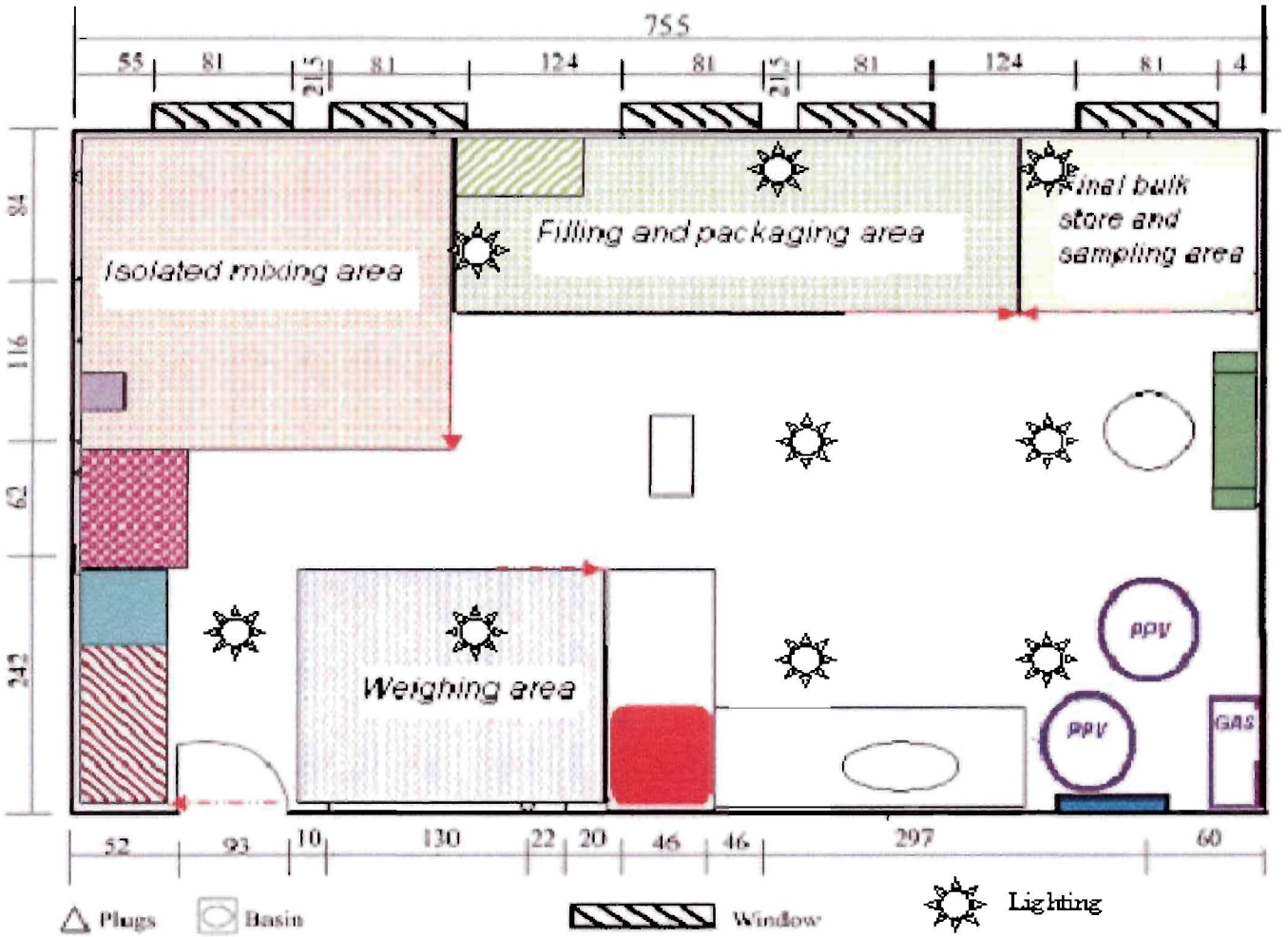


Figure 4.12 Placement of light fittings in the proposed theoretical design.

Table 4.1 Materials and finish selection for the pilot plant.

ARCHITECTURAL ELEMENT	FIRST CHOICE	SECOND CHOICE	THIRD CHOICE IF APPLICABLE
FLOORS	Isolation area: Surfaces should be smooth and cleanable. Sealed concrete with an epoxy coating or seamless vinyl are suitable chemically resistant coatings. Other areas: Standard construction is appropriate. Should include sealed concrete and epoxy coating.	Isolation area: Standard construction is appropriate. Typically, sealed concrete and epoxy coating. Other areas: Sealed concrete and coatings with a high level of wear resistance.	N/A
INTERIOR WALLS	Wall construction should be solid non-porous surfaces. Finish on smooth plastered walls: Epoxy paint, resinous coating. Area around basin: 3 x 2 m glazed white tile. Isolation area: A smooth, seamless glass surface that is easily cleanable. The division should be from floor to ceiling. Other internal barriers on site: Separated areas should have a smooth glass surface. These barriers should be from floor up to 2 m height (i.e. not to ceiling).	Standard construction is generally appropriate. Walls should be smooth with a finish appropriate to durability and cleanability requirements. Non-dedusting paint to be used. Area around basin: 3 x 2 m glazed white tile. Isolation area: Smooth glass surface. Floor to ceiling barrier. Other internal areas: Glass. Storage areas can be separated by wire mesh / chains or moveable partitions (plastic curtains).	N/A for isolation area. N/A for weighing area. Other areas: typical materials include wire mesh or gypsum board.

Table 4.1 Materials and finish selection for the pilot plant – continued.

ARCHITECTURAL ELEMENT	FIRST CHOICE	SECOND CHOICE	THIRD CHOICE IF APPLICABLE
CEILINGS	Materials: Cleanable and non-porous Rhino board / gypsum board finished with epoxy resin paint. Sealed (caulked in place), suspended grid systems.	Mylar, FRP, metal or other cleanable non-porous materials, finished with epoxy resin paint.	N/A
INTERSECTION DETAILS WALL / WALL; WALL / CEILING; WALL / FLOOR	Covered or splayed integral floor bases are suggested to enhance ease of cleaning and to protect wall bases when gypsum board is used. Rounded wall / wall and wall / ceiling joints are recommended to enhance ease of cleaning.	Standard construction details are generally appropriate.	N/A
WINDOWS	The windows of the isolation area have to be smooth-surfaced glass and totally sealed off. The windows in the other areas are also glass and sealed off provided that an air conditioner or adequate ventilation would be available for worker comfort. There should be no ridges or gaps between the window framework and the ceiling.	No alternatives for the isolation area are allowed.	N/A

Table 4.1 Materials and finish selection for the pilot plant – continued.

ELECTRICAL SYSTEMS	FIRST CHOICE	SECOND CHOICE	THIRD CHOICE IF APPLICABLE
LIGHTING	The location and design should be such that dust and foreign material accumulation is avoided. It should be recessed or flush mounted fluorescent fixtures. Intensity & colour: 75 W fluorescent white light. *Quantity and locations: To be advised.* Emergency lighting: To be considered.	Teardrop shaped fixtures may be appropriate. Intensity & colour: 75 W fluorescent white light. Quantity and locations: to be advised. Emergency lighting: To be considered.	N/A
GROUNDING	All wiring must be insulated. Grounding relays must be located in a recessed access panel. Equipment should be grounded (balances, PPV, microwave, filling machine and mixer).	N/A	N/A
COMMUNICATION SYSTEMS	Telephones should be installed in locations that are practical, accessible and not prone to accumulation of dust and foreign materials that may be source of contamination. These can be located in the open part of the processing area.	N/A	N/A

Table 4.1 Materials and finish selection for the pilot plant – continued.

ELECTRICAL SYSTEMS	FIRST CHOICE	SECOND CHOICE	THIRD CHOICE IF APPLICABLE
WIRING METHODS	Should allow for proper maintenance, including easy access to junction boxes and outlet boxes. Conduits and raceways should be labelled for ease of identification. Flush-mounted boxes are suitable.	Modifications for additional electrical sockets at particular points have to be made. These should follow the principal of minimal occupational safety risk and reduced contamination.	N/A
EQUIPMENT LOCATION	Balances will be located in the weighing area and the isolation area. Multiple power outlets are required in the processing area for the microwave, PPV and mixer. Power outlets in the mixing area: For mixer and refrigerator.	N/A	N/A

Table 4.2 Specifications of dedicated areas in the proposed facility.

AREA OF FACILITY	DIMENSIONS	FURNITURE / FITTINGS	CLOSURE	DOCUMENTATION
RAW MATERIAL STORE	60 cm x 240 cm	Cupboard with two doors, dividing the unit horizontally. The cupboard must be lockable and should fit flush to the floor. A thermometer should be present.	Cupboard should be moisture resistant.	Procedures for receipt, handling, sampling, release for approval and dispensing are to be set up to regulate handling of each raw material. A stock control and accountability system should also be put in place.
REJECTED GOODS STORE	60 cm x 100 cm	A cupboard or unit that fits flush to the floor.		SOP for goods rejected store.
RETENTION SAMPLE STORE	Proposed to be located in the analytical laboratory.	A cupboard dedicated to storage of raw materials, packaging components and final product samples.		SOPs.
ISOLATED MIXING AREA	164 cm x 250 cm	Windows: smooth, sealed and easily cleaned. Coloured glass can be used to control light.	The unit should be completely closed off from the rest of the manufacturing plant, i.e. from floor to ceiling.	Cleaning of this area requires special SOPs. Batch manufacturing documentation should reflect if the isolated area was used.

Table 4.2 Specifications of dedicated areas in the proposed facility – continued.

AREA OF FACILITY	DIMENSIONS	FURNITURE/FITTINGS	CLOSURE	DOCUMENTATION
FINAL BULK PRODUCT and SAMPLING AREA	150 cm x 188 cm	Stored materials can be separated from the rest by being kept in the demarcated area and with status labels on the vessels.	Windows should be kept closed when products are in this waiting area. A physical enclosure reduces the risk of contamination and mix-ups of process stage.	Sampling procedure to be in place.
FILLING AND PACKAGING AREA	356 cm x 188 cm	The materials for closure are not critical but should adequately distinguish this area from other areas. Windows must be sealed to reduce possible contamination during filling and packaging.	The type of closure can be partial, i.e. not up to the ceiling.	Procedures on regulating the filling and packaging material should be established.
WEIGHING AREA	200 cm x 170 cm	Should be enclosed.	Preferably glass and should be 2.0 m high.	The closure should prevent turbulence during weighing.
PHEROID PRODUCTION AREA	307 cm x 450 cm	Cupboards along side of the weighing area that extends at right angles to the fitting for the sink.		Batch manufacturing documentation. Equipment SOPs and cleaning SOPs.

Table 4.2 Specifications of dedicated areas in the proposed facility – continued.

AREA OF FACILITY	DIMENSIONS	FURNITURE/FITTINGS	CLOSURE	DOCUMENTATION
PRINTED PACKAGING MATERIAL STORE	Dedicated cupboard.	Cupboard should be constructed of moisture resistant material.	Lockable cupboard.	SOPs for receipt, approval and status labelling.
UNPRINTED PACKAGING MATERIAL STORE	Dedicated unit.	Dedicated unit within the packaging area.	Cupboard should be lockable and constructed of materials that will minimise possible contamination.	SOPs for receipt and approval. Status labels.
GOODS RECEIVING AREA	Located at office G14, this is opposite the pilot plant.	Desk and storage unit.	Lockable cupboard.	SOPs.
GOODS RETURNED STORE	Located at office G14, this is opposite the pilot plant.	Cupboard.	Lockable.	SOP and status labels.

4.3 Results of practical evaluation of the theoretical design

The theoretical design underwent various stages of qualification to ensure that the facility meets the requirements in terms of:

i. Process;

ii. Equipment;

iii. Regulations and GMP;

iv. Worker safety and worker comfort and

v. Architectural aspects.

All the above issues that were taken into consideration during the design stage constitute the design qualification. Upon investigating the practical aspects for installation, as planned in the theoretical design, various components were found to be impractical or not feasible.

The practical aspects are discussed below.

4.3.1 Practical challenges of the theoretical design

The presentation of the theoretical model design to "Lab & Air" (laboratory installation and air handling unit contractors) for quotations for the installation of an air handling system highlighted several difficulties. The problems with the proposed theoretical design are represented by a simplified theoretical model in Figure 4.13.

It was planned that areas would have different air pressures to achieve a pressure cascade that would enable containment of particulate movement both out of the facility and between areas within the facility. The central area is to have a more negative pressure with respect to the outer corridor area, but must be more positive with reference to the isolation area. Air pressure is to be regulated in the following areas corridor; weighing, central and isolation areas. An ISO 6 (1000 particles / cubic metre) level within the isolation area was planned with a more negative pressure on the inside relative to the central area to prevent outflow of particles. Air would enter the isolation area from the top, passing through a HEPA filter, and extracted at the bottom through another HEPA filter allowing for 80% recirculation of the air.

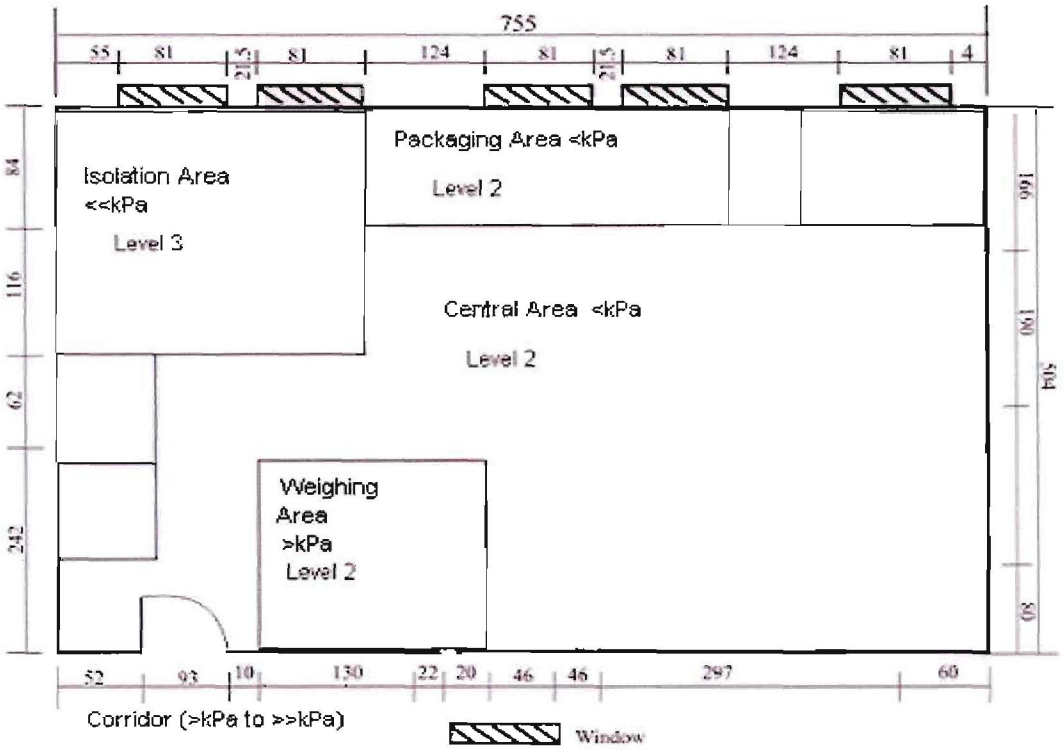


Figure 4.13 Outline of the theoretical model, indicating the required pressure differentials.

The weighing area should have a positive pressure relative to the central area such that there would be particulate movement out of the weighing area, thereby reducing the risk of contamination.

Christo Viljoen (consultant for Lab & Air) informed us on 07/11/2006 that the required pressure differentials appear to be possible theoretically, but isn't achievable in practice. Should the pressure differentials be applied in a space this small (see Figure 4.13), it would create turbulent airflow – thereby resulting in poor containment of particulates. Turbulence also hinders accurate measurement of both pressure and airflow, which are important predictors of particulate movement. The disruption of the predicted pathway of particulate movement will result in compromising the level of protection (ISO, 1995a & ISO, 1995b).

The quoted cost for installation of an air handling unit (AHU), capable of achieving the desired level of protection in the isolation area, was comparable to the cost of making the entire facility a cleanroom.

4.3.1.1 Rework on the theoretical model (Model 2)

An alternative would be to make the entire unit a clean room and fitting an AHU to service the entire pilot facility. A draft of model 2 is depicted in Figure 4.14. Because the AHU of the entire facility would effectively contain the movement of particulates, outwards, a dedicated isolation area becomes obsolete. The space previously occupied by the isolation area can now be used to expand the other dedicated component areas. The location of the diffusers and extractors of the AHU are shown in Figure 4.14.

When the project attracted more substantial financial backing, the additional funds available made it possible to re-locate the utilities in positions supportive of material, personnel and product flow. This resulted in extensive modifications to the theoretical model (Figure 4.14).

The design now features a larger raw materials store, a relocated cleaning area and a dedicated mixing area with gas tanks housed on the outside of the facility.

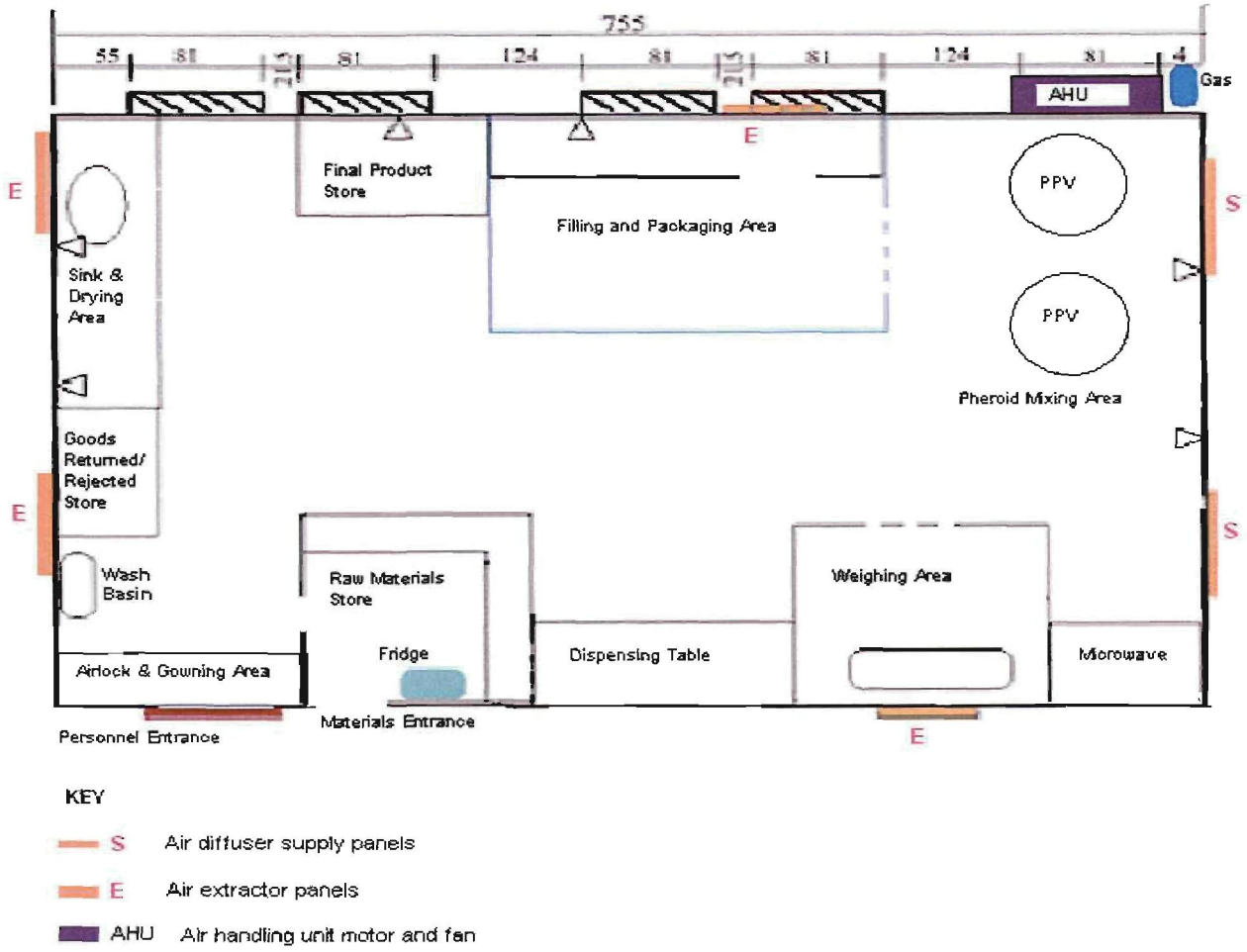


Figure 4.14 Model 2 (re-design of model 1).

4.3.1.2 Model 2 (re-designed model 1)

A bigger budget has made it possible to re-visit the design in terms of GMP and non-GMP components. The re-designed model 1 is referred to as model 2. The initial retention of utilities made it necessary to locate the various component areas of the facility in positions that were not conducive to the desired flow patterns for personnel, materials and products. The ideal flow pattern, shown in Figure 4.5 was used as a reference for the re-design process. Each of the changes is discussed below:

4.3.1.2.1 Personnel, material and product flow

i. Airlock: The personnel entrance will incorporate an airlock and gowning area. The airlock is 160 cm x 80 cm, will be an enclosed area featuring double doors. A lock system will prevent more than one door being opened at any given time. A basin

was included so that personnel would be able to wash their hands and glove before proceeding further. This is in keeping with the requirements for establishing a GMP manufacturing environment (Chapter 3, Figure 3.2).

ii. Raw material store: The store has been enlarged to 200 cm x 200 cm walk-in unit that will house a fridge and adequate shelving for quarantined and approved materials. The store will be locked to limit access to approved users. Dispatch of raw materials to the dispensing table will take place through a hatch. Raw materials will enter the facility from outside via a hatch (60 cm x 100 cm) that opens directly into the raw materials store, thereby separating the movement of materials and personnel entering the facility. All containers entering or leaving the facility will be cleaned to achieve the desired level of protection in the cleanroom. Material entry and transfer will be governed by relevant SOPs (Chapter 3, Figure 3.2).

iii. Dispensing area: This would be a table (120 cm x 80 cm) with cupboards beneath it for storage of dispensing utensils. Materials from the raw materials store will be transferred to the dispensing area via a hatch from the raw material store. Personnel would proceed to the dispensing area via the door.

iv. Weighing area: This will be an enclosed area of 180 cm x 150 cm. It will have a perforated weighing table which will house the balances.

v. Pheroid mixing area: This area (504 cm x 300 cm) will house the microwave, two PPV's and the mixer. The PPV will be located against the wall, near the fittings for the gas supply, electricity and potable water. Thus, movement of materials from the weighing area to the mixing area will follow a logical sequence. The storage area for the final bulk product has been merged with the mixing area, as the product would remain in the PPV for the duration of testing. Appropriate status labelling of the PPV will define the stage of processing. The mixing process will be governed the appropriate SOPs.

vi. Filling and packing area: This enclosed area of 250 cm x 150 cm will house the printed and unprinted packaging material stores. This area will also accommodate the filling machine and the necessary electrical utilities. The PPV, containing bulk products would be moved to this area for product filling and packaging.

vii. Final product dispatch area: This area (120 cm x 120 cm) will have cupboards to house the finished final product. Final product requisition and dispatch from the area would be governed by the necessary SOPs. The final product will be moved out of the facility in lockable bins that are carried out through the airlock by personnel.

viii. Cleaning area: Cleaning of utensils would take place in this area (200 cm x 80 cm) that houses a sink. A refuse bin for the disposal of empty packets, cartons and papers would also be located here.

ix. Rejected / returned goods store: This will be a lockable cupboard of 120 cm x 80 cm that will have shelving designed to hold at least 2 x 60 kg drums.

4.3.1.2.2 Airflow

The rate and direction of airflow contribute significantly to the achievement and maintenance of the desired level of protection in the facility (ISO, 1995a & ISO, 1995b). Figure 4.14 shows the location of the supply of HEPA filtered air as coming in from the top of the wall of the Pheroid mixing area. This location was chosen so as to provide the "cleanest" (from HEPA filter) air to the areas requiring the highest level of protection. Because the movement of air would be from one end (mixing area) of the facility towards the other end (cleaning area), air-borne particulates would be carried away towards the area requiring the lowest level of protection (cleaning area). The contaminated air would then be extracted from the cleaning area via extraction panels located on the far wall.

The weighing area has an air extraction panel below the perforated surface that extracts air downwards, preventing particulates generated here from contaminating other areas. The extracted air will also pass through a HEPA filter to prevent particulates from escaping into the outside environment. The chosen airflow rate constitutes 20 air changes per hour (ISPE, 1996). In Figure 4.14, the orange bars / panels marked "S" indicate the diffuser supply panels, whilst the orange bars marked "E" refer to the air extraction panels.

4.3.1.2.3 Architectural and structural components

The structural components, such as the materials for the ceiling, walls, floors and enclosures, would remain the same as in Table 4.1 of the theoretical model (model 1).

4.3.2 Practical challenges of model 2

The re-designed model (model 2), as presented in Figure 4.14, was evaluated by SSI consulting engineers. Because the re-design process took place in consultation with the previous evaluator (Lab & Air), an independent consultant had to evaluate model 2.

Deryck Smith (SSI consultant engineer) suggested on 16/11/2006 that, given the size of the facility, it may be more practical to operate the entire facility as a clean room at ISO 7 (10 000 particles per cubic metre), thereby still achieving the desired level 2 and 3 protection for production of Pheroid products. Problems encountered with model 2 were predominantly related to the AHU. The following challenges were identified:

i. The locations of the diffuser and extractor panels, on opposite walls, result in horizontal airflow at the same height as the panels. This would offer little or no protection against containing particulates for surfaces and processes below.

ii. The proposed number of air changes would not be sufficient to achieve the required level of protection.

iii. The number and type of diffuser panels as well as the air flow pattern would not be able to achieve the required level 3 or level 2 protection.

iv. The ISO level of the airlock should be the same as the protection level required in the facility (ISO, 1995a & ISO, 1995b).

v. Facility parameters that need to be controlled are temperature, humidity, air cleanliness, room pressure, air movement and lighting. These are all integral to achieving and maintaining the required room conditions. The absence of an air cooling system, with the proposed AHU in model 2, may result in a compromised operational environment. This could affect product quality, especially when the environmental temperatures may affect the storage conditions of raw materials, in-process products and final products.

vi. An absence of pre-filters would result in high maintenance costs, because expensive HEPA filters would have to be replaced more frequently.

4.3.2.1 Rework on model 2

The reworked model 2 resulted in model 3. Minor changes were made in the arrangement of the facility component areas and to structural components (ceiling). This was done to make provision for an airlock with the same level of ISO protection as the facility itself. A more detailed look into the HVAC system, and its impact on containment and the operational aspects of the facility environment, initiated the modifications to model 2. Table 4.3 provides a summary of the component areas of model 3 and outlines the specifications for utilities, cupboards, fittings and the HVAC system. The changes made are discussed below.

4.3.2.1.1 Personnel, product and material flow

i. Airlock: The airlock would be widened so that both doors can open inwards into the airlock. This would assure movement of air into the airlock for both entry and exit. The pressure in the airlock should be lower than that in the outside corridor, as well as the pressure in the central space of the facility. This would create a bubble pressure cascade system, allowing movement of air into the airlock (WHO, 2006). The airlock should also have adequate space to have a step over bench from the area of the where gowning takes place to the area of entering the facility central space. The doors of the airlock should be wide enough to allow the entry of the PPV – no less than 1.5 m.

ii. Raw material store: The size of this area has been reduced to 150 cm x 200 cm to compensate for the bigger airlock and wider door.

iii. Weighing area: The length of this area has been reduced to 150 cm and the front is no longer closed off. The weighing bench would be sturdy and perforated. There will be an extractor below the bench that will channel the air towards a central exit equipped with a HEPA filter. The extractor will be more efficient in achieving the desired negative pressure in a smaller area. The negative pressure assists inward airflow, while the extractor removes these particulates hence enabling containment. A diffuser panel will be located in the region of the weighing area, but not directly above the balance as it may create turbulence which will affect accuracy. The operators would have to wear masks and gowns to avoid exposure to any of the API's (Chapter 3, Figure 3.2).

iv. The dispensing area: This area need not be enclosed, but if it were, it would need to be easy to open to allow for cleaning and ventilation. Because the size of the weighing area was reduced, a longer table can be fitted into the dispensing area. The table will be large enough to accommodate another cupboard below it.

v. A design giving the dimensions and locations of the various component areas is depicted in Figure 4.18.

4.3.2.1.2 Airflow

Proposed changes to the AHU include:

i. The diffusers will be moved from the wall to the ceiling. This will facilitate downward movement of the air. The rationale for this change stem from the airflow pattern, the rate of air change and the achievement of the desired clean room status. The current model 2 indicates horizontal flow of air across the cleanroom which can be represented by Figure 4.15. This uni-directional flow of air from the top across the room may not allow the HEPA filtered air to reach all areas of the facility. If the extractors are located at the same level as the diffusers, the airflow would move above and across all the component areas and hence will not provide the level of protection as virtually no clean air would be available at the operational level. Should the extractors be located at a lower level, the areas requiring the clean air would not receive it as the air would be passing over the mixing and filling areas, but providing clean air to the cleaning area and dispatch area where it is not needed. Hence, the recommendation to have several diffusers from the ceiling supplying clean air over the areas requiring it. The extractors would be located at the lower end with more extractor points at the opposite end.

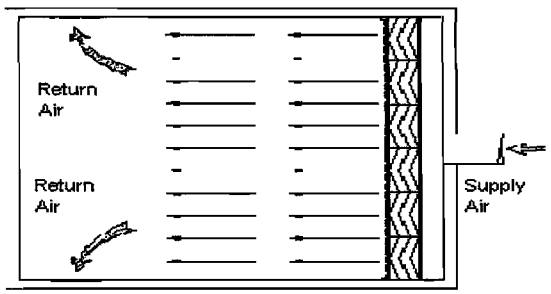
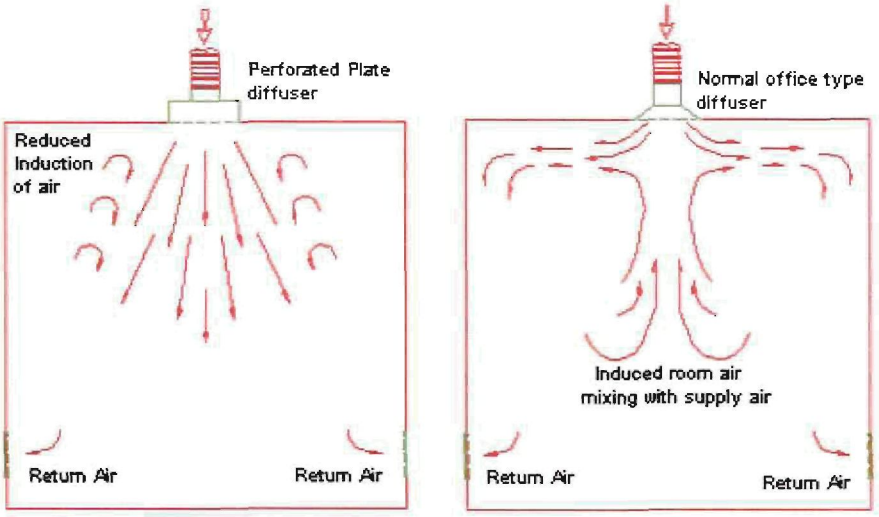


Figure 4.15 Uni-directional air flow pattern adapted from WHO (2006).

ii. The two wall-mounted diffusers will be replaced by four diffusers distributing HEPA filtered air (turbulent flow) from the ceiling downward. The various locations of the diffusers are shown in Figure 4.19. One diffuser will be located over the Pheroid production area, another above the weighing area, one in the airlock and one over the region of the filling and central area. The selection of the type of diffusers to be installed is dependent on the airflow pattern required to best achieve the desired level of protection. A perforated diffuser, creating turbulent airflow, will be most suited to the facility. Figure 4.16 (a) illustrates the airflow created using a perforated plate diffuser that supplies air from the top downwards. In this scenario, the risk of contaminants being spread is reduced, because there is little mixing of room air with supplied air. Figure 4.16 (b) shows the use of a normal office-type diffuser in which the room air mixes with the supply air resulting in higher risk of particulate contamination.



(a) Perforated plate diffuser (b) Normal office type diffuser

Figure 4.16 Types of diffusers adapted from WHO (2006).

iii. SSI engineering consultants calculated the air supply, needed to obtain an ISO 7 class facility, as follows:

- Air Supply = Room Volume X Air change / hour
  = (2.4 m x 7.55 m x 5.00 m) x 40 / 3600 s = 1.00 m^3/s

- To achieve ISO 7 throughout the facility we require 40 air changes per hour. Note: SSI have indicated that although 4 to 20 air changes are recommended in the ISPE (1996) and ISO guidelines (1995a & 1995b), it is their experience that 40 air changes would be required to achieve a minimum of ISO 7.

iv. The air inlet will have primary and secondary filters that will pre-filter the air before it passes through the HEPA filter. This will increase the lifespan of the HEPA filter. The filters are shown in Figure 4.17. In the absence of pre-filters, the HEPA filter would be burdened with the full filtration load – particulates would quickly block the movement of air, thereby compromising the capacity and integrity of the HEPA filter. The HEPA filters are very expensive and it would be more cost-effective to regularly replace pre-filters, rather than the HEPA filters themselves.

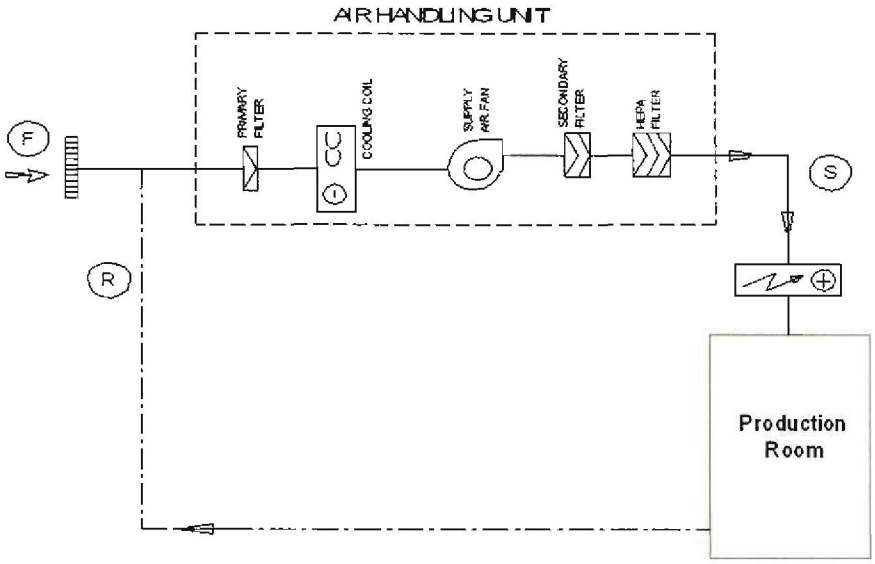


Figure 4.17 Components of an air handling unit of a recirculation system adapted from ISPE (1996).

v. The extraction panels in the weighing area, airlock / change room and the desk area will be located lower down.

vi. The air exiting the facility through the ducting will pass through a HEPA filter to ensure that it is free from contaminants.

vii. It would be more cost-effective to re-circulate air, adding only 15-20% fresh air per cycle. The conditioning and filtering of fresh air would demand a more complex and efficient AHU, whilst if a greater percentage of air (80%) is re-circulated, a simpler system would suffice as most of the air would already have been filtered and cooled / heated.

viii. The AHU will be housed outside of the facility. Ducting will be located in the ceiling. The necessary changes will have to be made to the ceiling. Figure 4.19 shows the locations of the diffusers and ducting of the HVAC system (model 3).

4.3.2.1.3 Architectural and structural components

i. The ceiling will be dropped by 20 cm to accommodate the ducting for the diffusers. Thus, the new ceiling height will be 2.4 m from the ground.

ii. Cupboards, surface layout and other components: A design representing the organisation and location of the cupboards and dedicated components of the facility is shown in Figure 4.20.

iii. Table 4.3 provides a breakdown of the various dedicated areas, including their respective structural components as depicted in Figures 4.18, 4.19 and 4.20.

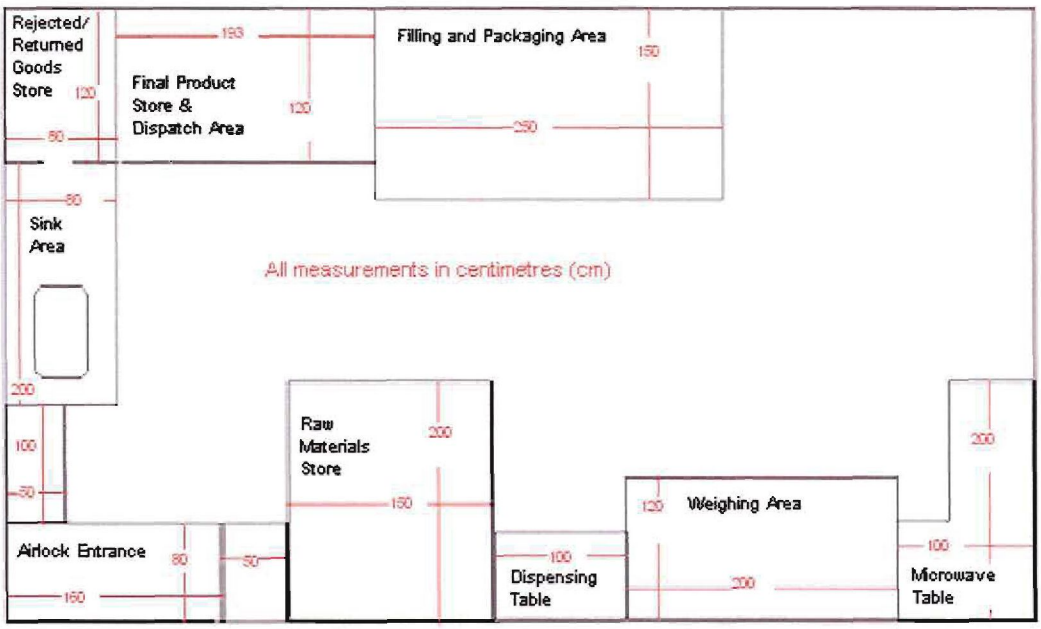


Figure 4.18 Design of the facility as cleanroom, with dimensions (model 3).

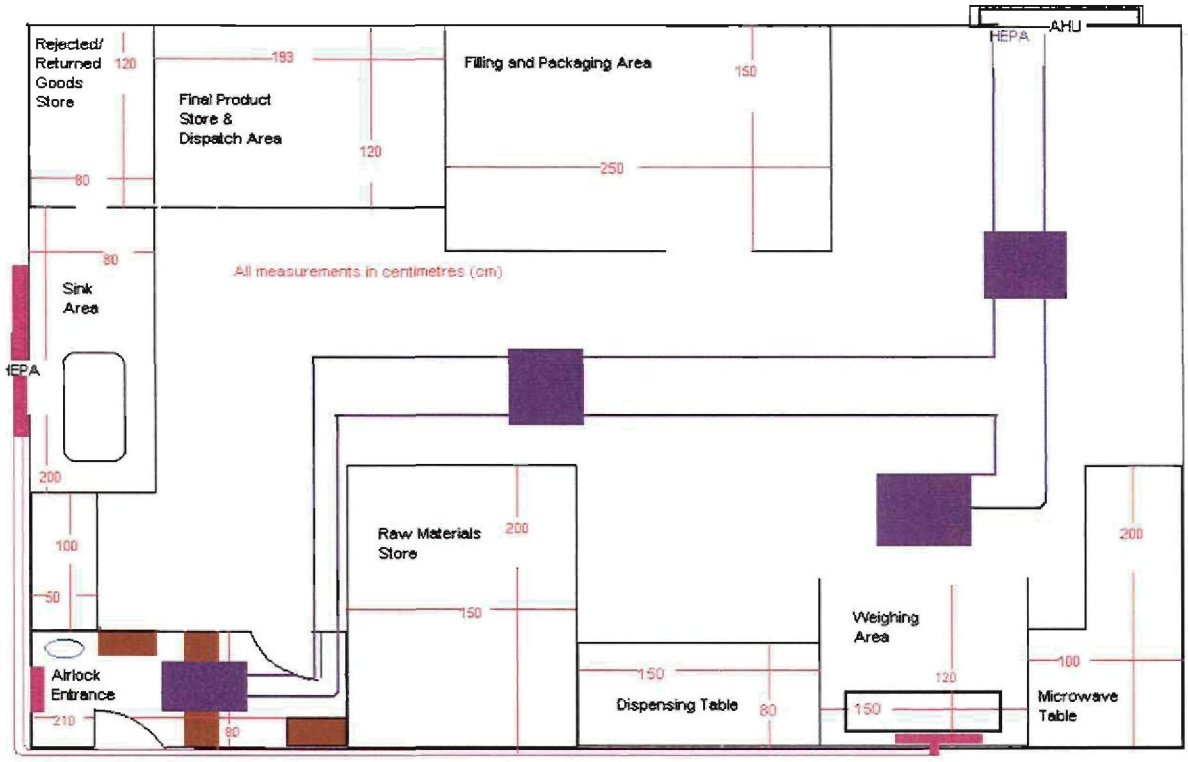


Figure 4.19 Design of the pilot facility depicting AHU, filter and extractor locations (model 3).

Key to Figure 4.19

	Air flow from the AHU, through a HEPA filter, into ducting and distribution channels. The squares just outside the weighing area, above the filling area, in front of the raw materials store and in the airlock represent the diffusers.
	Air outflow ducting and extraction areas, that will eventually move air out through one HEPA filter.
	Clothes / coat rack and the step-over bench (central).

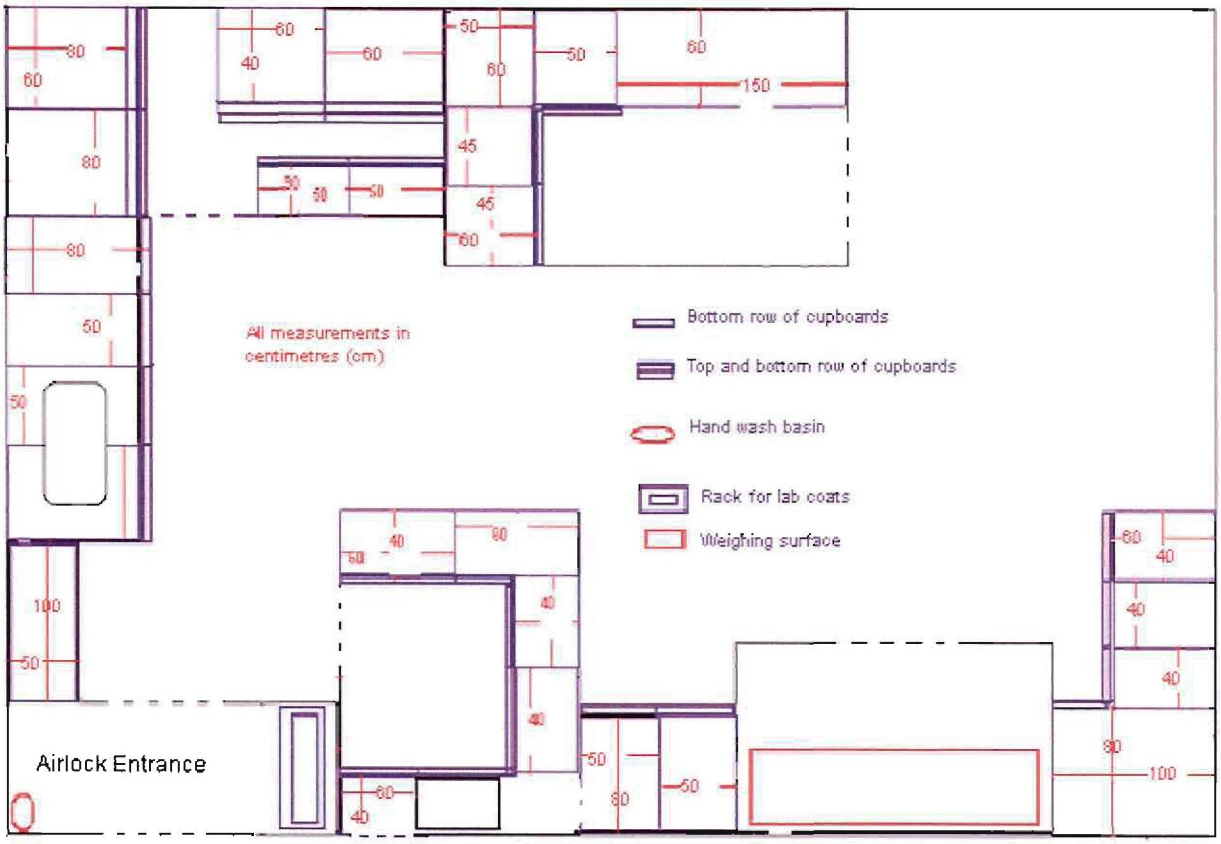


Figure 4.20 Design of the pilot facility depicting cupboard layout and dimensions.

Table 4.3 Outfitting of dedicated component areas.

AREAS	**UTILITIES /FITTINGS**	**CUPBOARD REQUIREMENTS** (All heights are 1 m from ground all measurements are in cm)	**HVAC**
AIRLOCK	Entrance: Outer door - Security and control mechanism. Inner door - swing open or sliding mechanism. Hand basin with water supply. Lighting: 1 x fluorescent ballast.	Coat rack of dimensions 50 x 80 x 150 cm (above ground).	Air supply from perforated diffuser located in ceiling. The air extraction vents are located at the bottom of the wall adjacent to the entrance. To achieve ISO 7.
WORK TABLE	Lighting: 1 x fluorescent ballast above work desk. 2 x electrical sockets for computer.	Desk: No more than 50 x 100 cm. Should consider a retractable or fold-away surface.	Subject to room HVAC, an air extractor point may be installed below the desk.
SINK AREA	Lighting: 1 x fluorescent light above this area. Sink: Plumbing requirements for installation of water supply; drainage from sink and installation of mini heater / geyser. Tiles on side of wall against which sink is fitted (reduce moisture penetration through wall).	Surface: 200 x 80 cm. Sink: itself 80 (L) x 50 (W) and 40 (D) cm. Four cupboards below sink: each 50 cm wide. Each cupboard will be divided into a top and bottom shelf.	Lowest level of protection needed at cleaning area. Extractor panels / ducts located at this end.
REJECTED GOODS STORE	Lighting: 1 x fluorescent light above / outside this area.	Floor-to-ceiling cupboards: 240 (H) x 60 (W) x 80 (D) cm. These cupboards are divided into upper and lower sections. Lower section: 100 (H) x 60 (W) x 80 (D) cm. Upper section: Divided into 3 shelves.	Subject to overall room protection.

Table 4.3 Outfitting of dedicated component areas – continued.

AREAS	UTILITIES /FITTINGS	CUPBOARD REQUIREMENTS	HVAC
FINAL PRODUCT	Lighting: 1 x fluorescent light. 1 x electrical socket.	2 x cupboards of 60 (W) x 40 (D) cm. Both cupboards will be divided into a top and bottom section, and each section will have 3 shelves. A dispatch surface and, below that, two cupboards of 50 (W) x 30 (D) x 100 (H) cm.	Subject to overall room protection and temperature.
FILLING & PACKAGING	Lighting: 1 x fluorescent light. 3 x electrical sockets.	The work surface / table in this area will be 60 cm wide and L-shaped (150 x 200 cm in length). Cupboards below the work surface: 2 units of 45 (W) x 60 (D) cm as well as a corner unit of 50 (W) cm 60 (D) cm - refer to figure 4.20. The corner unit will be used as a store for unprinted packing material and should not be subdivided. One of the 45 x 60 cm units will be converted to drawers (for storage of printed packing material). The other can be divided internally into two shelves.	As the area is closed off, a dedicated diffuser (to supply HEPA-filtered air) will be located in the ceiling above the filling area to maintain an ISO 7 level of protection. An extractor panel will be located near the bottom of the wall.
MIXING AREA	Lighting: 3 x fluorescent lights in this area. 4 x electrical sockets. Adaptation for gas inlet system and tubing. Water supply connectors to water jacket of PPV and drainage directly from vessel (i.e. closed system).	No cupboard.	A dedicated diffuser will supply HEPA-filtered air to this unit. It will reduce the risk of contamination during mixing by supplying clean air. The diffuser will be located above the mixing area.

Table 4.3 Outfitting of dedicated component areas – continued.

AREAS	UTILITIES /FITTINGS	CUPBOARD REQUIREMENTS	HVAC
MICROWAVE	Lighting: 1 x fluorescent light. 1 x electrical socket.	An L-shaped corner unit with one side being 200 (L) x 60 (W) cm, and the other side 100 (L) x 80 (W) cm forming a corner unit. The three cupboards are 40 (W) x 60 (D) cm and each is divided into two shelves. There will also be a corner unit.	This region will benefit from clean air supplied by the mixing area diffuser and the weighing area diffuser-reduced risk of in-process contamination.
WEIGHING AREA	Lighting: 1x fluorescent light. 2 x electrical sockets.	The sturdy work surface will be 150 (L) x 60 (W) cm.	A diffuser supplying clean air will be located in the ceiling. It will not be installed directly over the balances, but rather 0.5 m to the side. This should minimise the effect of turbulence on weighing accuracy.
DISPENSING TABLE	1 x electrical socket.	The table will be 100 (L) x 80 (W) cm with two cupboards (50 x 80 cm) below it. One cupboard will be converted into drawers and the other will be divided into two shelves.	Subject to overall room protection.
RAW MATERIALS STORE	Lighting: 1 x fluorescent light. 2 x electrical sockets, one of which is for the fridge.	A C-shaped cupboard with two sides being 150 (L) x 40 (W) cm and the other side 160 (L) x 40 (W) cm. The shelving on left would not have any internal divisions so as to house a bar fridge. All other shelving would be 40 (W) x 75 (D) cm.	Subject to overall room protection and controlled temperature.

4.3.3 Evaluation of model 3

An evaluation of the model 3, by SSI engineering consultants and the NWU physical infrastructure planning unit, was done to establish its feasibility in terms of engineering, construction and maintenance. Arno de Beer and Elza Moorcroft (NWU infrastructure and planning unit) informed us that an emergency exit and emergency shower ought to be included in the design.

An emergency exit and retractable emergency shower were added to the design. Although these measures are generally not required for facilities not producing API's, their inclusion is prescribed by the institution (NWU). SSI engineering consultants reported that the diffusers supplying clean air to the weighing area and the Pheroid mixing area, are too close to each other and that this would create turbulence that may interfere with the accuracy of the balances.

4.3.3.1 Re-design of model 3 (model 4)

Following the evaluation of model 3, changes were made to the design (that will now be referred to as model 4).

i. An emergency shower will be located in the mixing area. This location has been identified as the area posing the highest occupational risk. The emergency exit (81 x 200 cm) will also be located in this area in a space previously occupied by a window. The door will open outwards to provide a means of escape from the building. Seals around the door will prevent leakage of air into or out of the facility, thereby maintaining a controlled environment. Figure 4.21 shows the location of the emergency exit and shower.

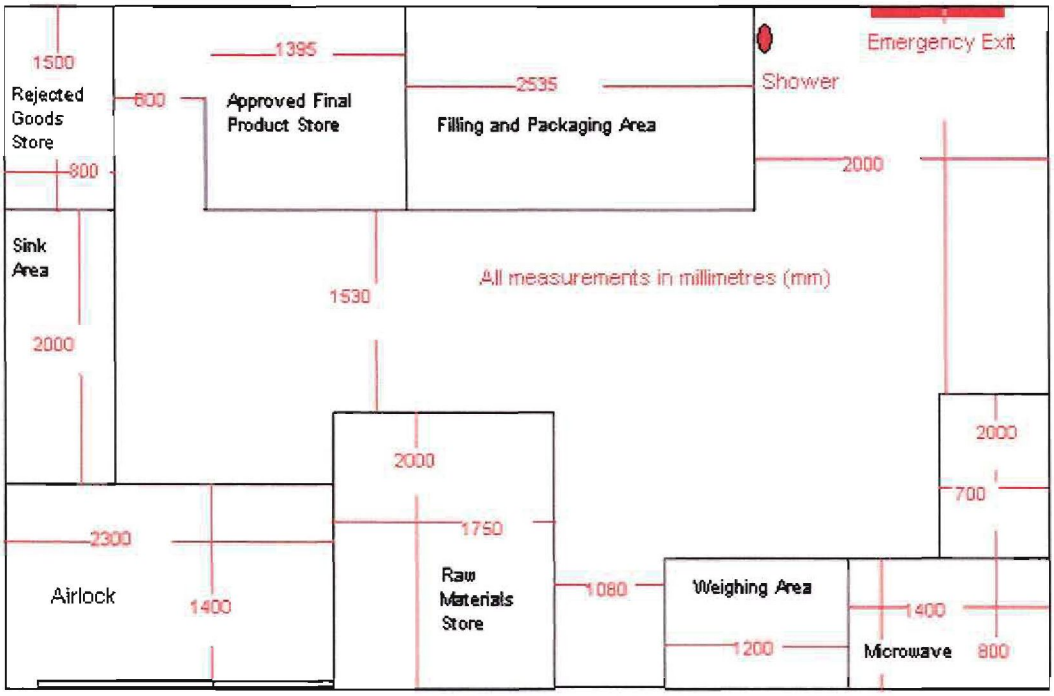


Figure 4.21 Representation of the emergency exit and shower location (model 4).

ii. The turbulence, caused by two diffuser panels in close proximity, is addressed by reducing the number of diffusers from four to three with one large diffuser supplying clean air to both the weighing and mixing areas. Placement of the diffusers is shown in Figure 4.26.

4.3.3.2 Layout of individual components included in the final facility design (model 4)

The reworked model 3, now referred to as model 4, was evaluated by the NWU infrastructure and planning unit in consultation with SSI. The consensus reached was that model 4 would meet the engineering, construction and manufacturer's requirements. The design should be used to draft the architectural plan. A series of Figures (4.22 to 4.27) show the layout of the facility, including component areas, utilities, structural components and the AHU. A design report can be compiled from the specifications outlined for each of the components. Table 4.3 provides an outline of the specifications.

4.3.3.2.1 The layout of component areas is shown in Figure 4.22 below. Measurements are given in millimetres.

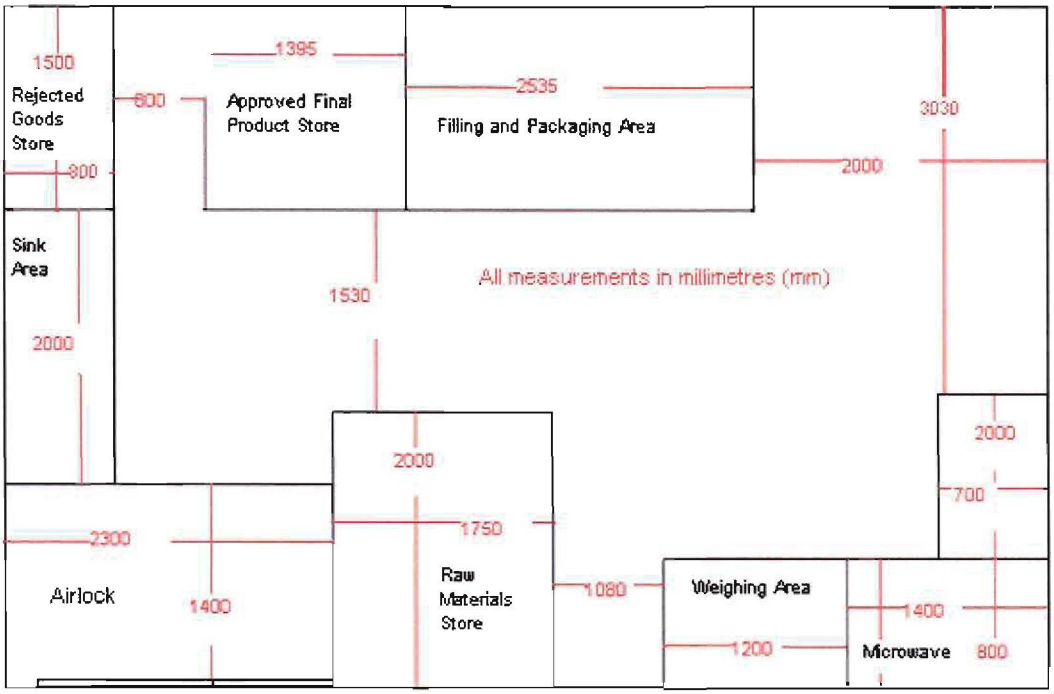


Figure 4.22 Layout and dimensions of the respective component areas of model 4.

4.3.3.2.2 Layout and dimensions of cupboards

Figure 4.23 Dimensions and cupboard layout of model 4.

4.3.3.2.3 The placement of light fittings

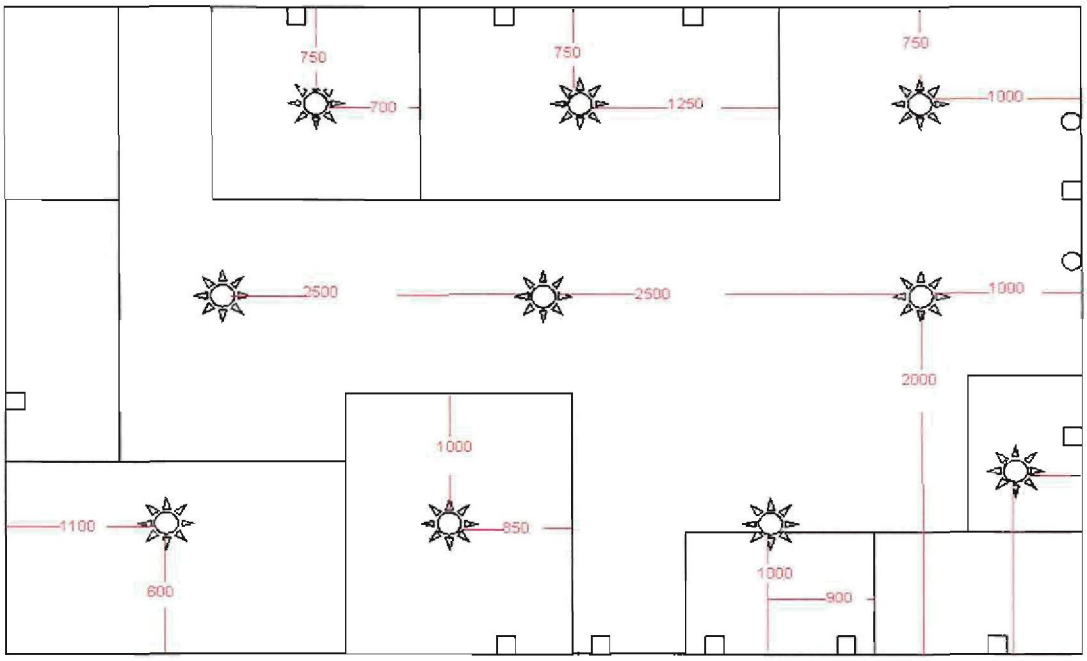


Figure 4.24 Placement of light fittings (model 4).

4.3.3.2.4 The placement of the electrical sockets (represented by little squares) is shown in Figure 4.25. The two small circles represent dedicated three-phase electrical connections for the Pheroid pressure vessel.

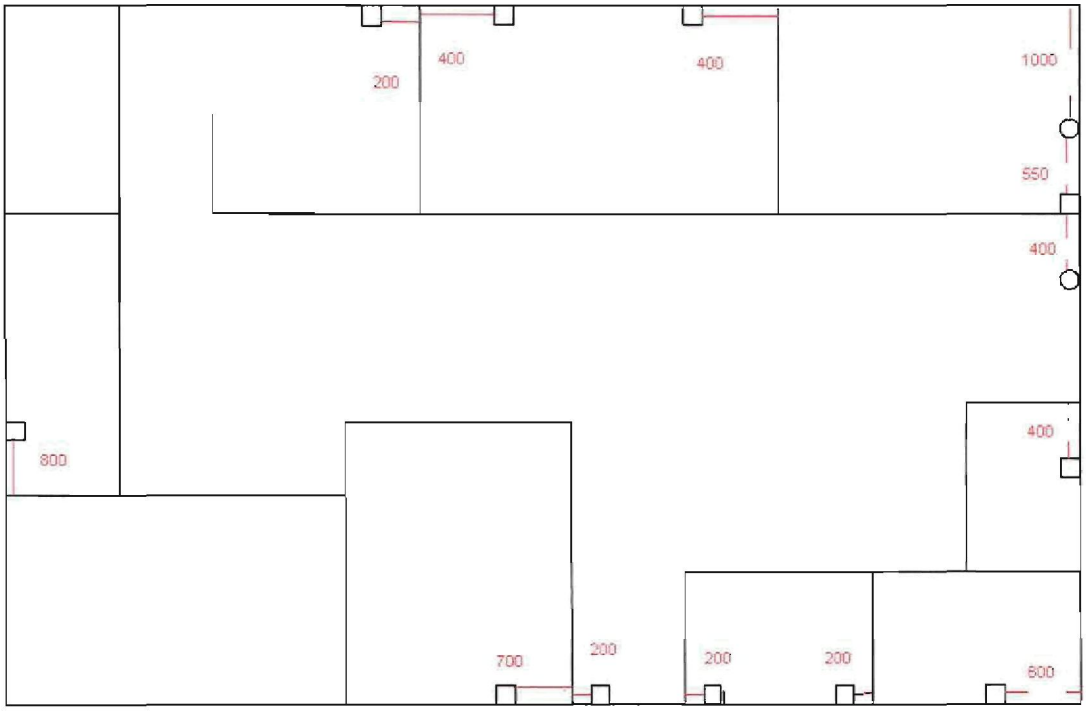


Figure 4.25 Placement of electrical fittings (model 4).

4.3.3.2.5 **The layout of the air handling unit** is represented in Figure 4.26. The air supply conduits / tubing are shown in blue. The squares represent supply vents in the mixing, packaging and airlock areas of the facility. The ducting carrying the extracted air (which passes through a HEPA filter before re-circulation) is shown in pink. The pink squares represent the extractor ports - these are located in the packaging area, weighing area, airlock and rejected goods area.

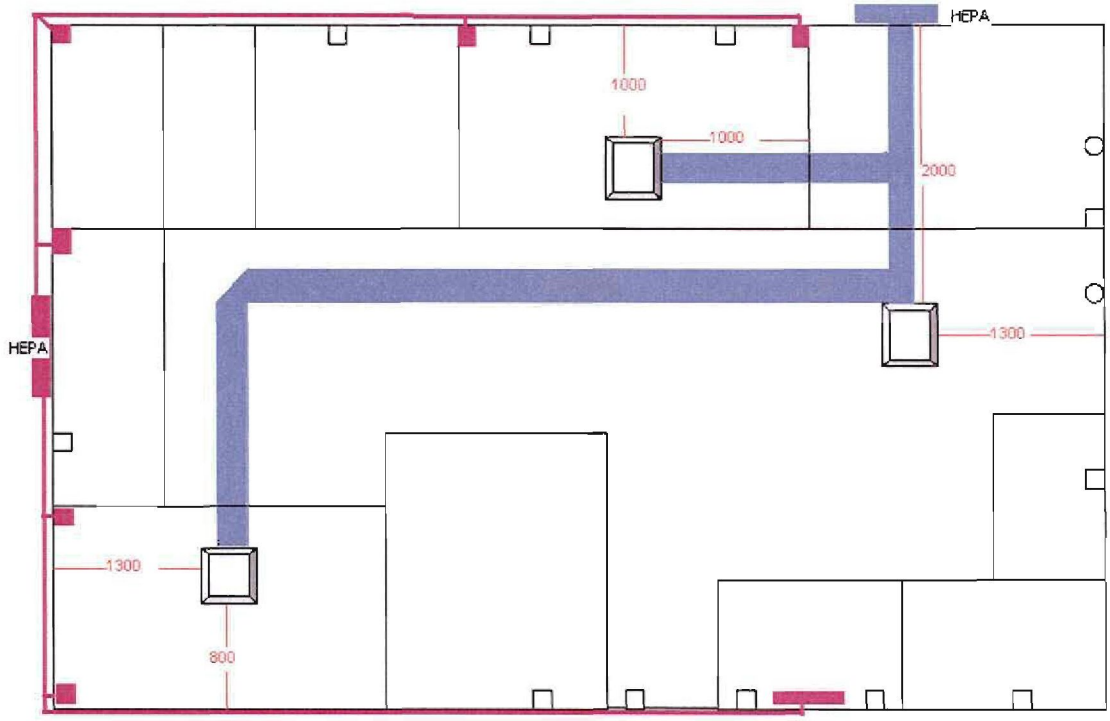


Figure 4.26 Layout of HVAC systems in the final design.

4.3.3.2.6 **Placement of the doors within the facility** is represented in Figure 4.27. With the exception of the emergency exit (red), doors are shown in green. The door between the airlock and the cleanroom area will have two portions consisting of a 900 mm swing door and a 700 mm lockable panel. The 900 mm door will be used for normal personnel movement. The 700 mm portion will only be opened, together with the 900 mm portion, when the Pheroid vessel/s needs to be transferred into or out of the facility (during servicing of the vessels).

Figure 4.27 Location of doors in the final design.

4.4 Facility Cost

In the pharmaceutical industry, investment in manufacturing facilities would be preceded by a life-cycle cost analysis. This analysis takes into consideration all facility specific costs divided by the estimated lifespan or estimated period of service of the facility. This enables companies to prioritise and to determine the feasibility of the investment in terms of capital returns (Signore, 2005). In the case of a pilot facility, the costs have to be weighed against the period over which trial batches will be produced, because the facility will not directly generate any income. The pilot facility will have the added benefit of providing a learning experience for students. Neither this learning experience nor the data generated can be quantified in monetary terms.

4.4.1 Commissioning and life-cycle costs

The cost of commissioning was influenced by user requirements, process requirements and regulatory requirements. Due to the limited space available, modifications had to be made to equipment and the architectural layout. This added to the overall costs.

The process of attempting to integrate GMP requirements with user and process requirements, at the lowest possible cost, is illustrated in the presentation of models 1-3. The commissioning cost of a GMP facility will be greater than that of a research laboratory that need not adhere to good manufacturing practices.

The final layout of the pilot facility takes into consideration material, personnel, product and waste flow - hence the demarcation of dedicated component areas within the facility.

4.4.1.1 The effect of non-GMP technology on commissioning and life-cycle cost

Table 4.4 illustrates the impact the use of non-GMP technology (individually and combined) has on facility commissioning as well as life-cycle costs (maintenance costs). Closed processing was requested by the user, but it is also safer for the operator as well as the environment.

Table 4.4 Non-GMP technology selection versus facility cost.

Cost Implications for closed processing.	Model Number	Non-GMP Technology						Overall Cost	
		Equipment	Architectural	Isolator unit	HVAC	Process & Support Utility	Electrical fitting	Commissioning	Maintenance
	1	⇧	⇧	⇧	Not applicable	⇩	⇩	⇧	⇧
	2	⇧	⇩	Not applicable	⇧	⇧	⇧	⇧	⇩
	3	⇧	⇧⇧	Not applicable	⇧⇧	⇧	⇧	⇧⇧	⇩⇩
	4	⇧	⇧⇧⇧	Not applicable	⇧⇧	⇧	⇧	⇧⇧	⇩⇩

Key to Table 4.4.

⇧	High Costs
⇩	Low Costs

4.4.2 Life-cycle cost versus technical complexity

The design process has resulted in the development of models of increasing complexity. In this project it was noted that the cost of commissioning increased with the increased complexity of the AHU. It was further noted that as the complexity of the AHU increased that the estimated overall cost of maintenance decreased, hence indicating a proportionate decrease in the life-cycle cost. This relationship can be illustrated with a graph of "life-cycle cost" versus "technical complexity" (ISPE, 1998). Figure 4.28 illustrates the ideal balance between these factors and also indicates where the different design models would rate.

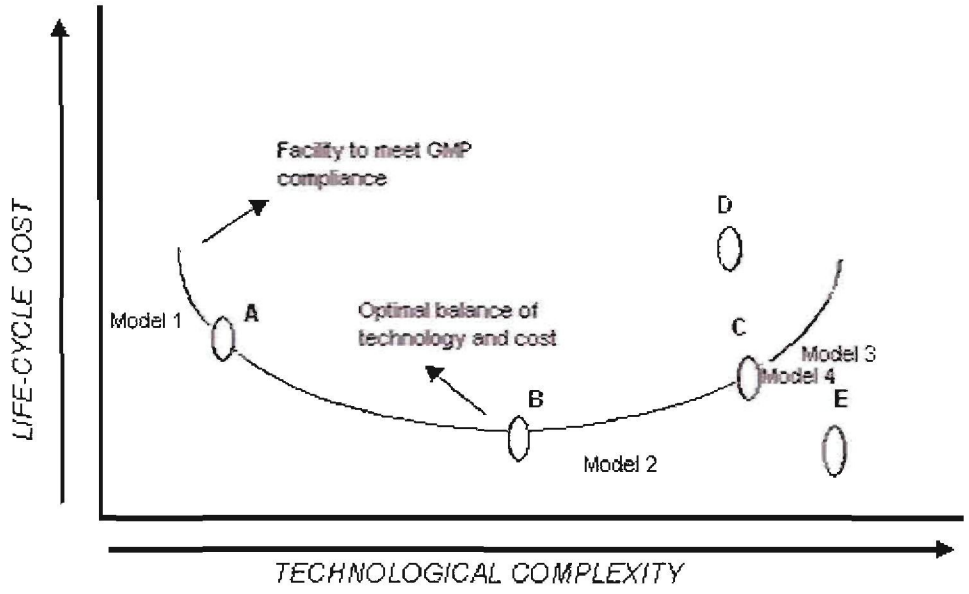


Figure 4.28 Life-cycle cost versus technical complexity (adapted and from ISPE baseline guides of 1998).

The curve (Figure 4.28) represents the minimum life-cycle cost, at any given level of technological complexity, for achieving GMP compliance. If all other contributing factors are ignored, it can be assumed that GMP compliance is possible if the facility falls on or above the curve.

Five theoretical scenarios (A - E) are shown in Figure 4.28:

i. **A**: A GMP compliant facility of relatively low technological complexity. Life-cycle costs are high.

ii. **B**: This facility achieves GMP compliance at a level of technological complexity that minimises life-cycle cost. This is the ideal scenario.

iii. **C**: GMP compliance is attained at higher level of complexity, and with a higher life-cycle cost.

iv. **D**: Although GMP compliance is attained at a higher level of technological complexity, the life-cycle costs are much higher than in scenario C.

v. **E**: Even though this facility is sophisticated with a low life-cycle cost, it is not GMP compliant. Some sophisticated technologies are designed for production requirements with little or no focus on GMP.

It is important to note that the interpretation of the life-cycle cost was limited to the assumption that the extent of maintenance would be the only factor that would influence the life-cycle cost.

4.4.3 The effect of non-GMP technology on commissioning and life-cycle cost of the facility models

The impact of non-GMP technology on the commissioning and life-cycle costs of the four models can be deduced from Table 4.4 and illustrated on Figure 4.28.

Model 1: Shows high commissioning and maintenance costs for the model having the isolation area. The isolator technology therefore implies a high life cycle cost.

Model 2: The air handling system of this model is technologically more advanced than the isolator technology and indicates similar costs of commissioning. It has an advantage of low maintenance and hence implies a low life-cycle cost compared to model 1.

Model 3: The HVAC system of this model is more technologically complex than the isolator and air handling unit technology of models 1 and 2. The commissioning costs are much higher than that of model 1 and 2. The maintenance costs are however much lower than the first two models implying that this model would have a much lower life-cycle cost as well.

Model 4: The same HVAC technology is applied in this model as with model 3. This model operates with fewer diffuser panels hence slightly reducing the commissioning costs and has similar maintenance and hence life-cycle costs as model 3. The reduced

number of diffuser panels in model 4 enables achievement of the desired level of product protection and hence greater GMP compliance.

4.5 Conclusion

The design process followed to obtain the most suitable facility design in terms of the user, process and regulatory requirements included the following chronological steps:

i. establish the desired requirements,

ii. determine the feasibility of the project based on the requirements,

iii. draft a facility design based on the desired requirements,

iv. evaluate the design for practical suitability and GMP compliance,

v. rework the model if necessary,

vi. repeat stages iv and v until a model that satisfies all the desired requirements are met.

The site allocated was unsuitable in terms of worker safety, production and GMP requirements. A recommendation to contain most of the processing in a specialised processing vessel enabled continuation of the facility design process.

Three revisions and reworks were necessary to finally assemble all the respective specifications that ultimately defined the layout of the final design. Adequate financial support to ensure commissioning and maintenance had to be considered as each of the models involved a greater degree of technological complexity. Considerable choices emerged during the design process indicating that various facets of design can be manipulated to best achieve the desired requirements.

The final model (model 4) features an ISO 7 class airlock, dedicated component areas, a PPV and an HVAC system that collectively contributes to achieving the desired user, process and regulatory requirements. Compared to the previous models, model 4 is technologically more complex, requires lower maintenance implying a lower life-cycle cost, but has a higher commissioning cost.

Chapter 5

PROPOSED ARCHITECTURAL DESIGN, RECOMMENDATIONS AND CONCLUSION

5.1 Introduction

This chapter discusses the final architectural plan for the Pheroid pilot facility derived from specifications and representations of the draft layouts of the various components of model 4 (Chapter 4). The conclusion and recommendations form part of this chapter.

5.2 Proposed architectural design

A final design has been drawn up in consultation with engineers and construction commissioners. The approach followed included re-modelling or re-working of the design based on feedback from all parties involved. Table 4.3 gives the specifications of components of the facility. Figures 4.21 - 4.27 show the layout and dimensions of utilities and component areas. These plans were consulted in the drafting of the final blueprint for the pilot facility. Figure 5.1, an architectural design plan, was drawn up by the NWU architectural unit in consultation with the manufacturer and the physical infrastructure and planning unit. The copy of the plan in Annexure B is an A3 enlargement that improves legibility of fine print.

The FDA audits facility design plans, whereas this is not a function of the South African regulatory authority. Hence, the pathway followed with this design process differs from the one described by Del Ciello (2005). In this case, the conceptual design was sent to the engineers and the NWU's commissioning team for comments. As there have been no further changes or recommendations, this design plan will be submitted, together with quotations, for financial auditing and will ultimately be used as a component of design qualification during commissioning of the facility. The equipment (PPV) design qualification and installation is integral to the GMP compliance of the proposed facility. The engineers who will install the HVAC should provide the necessary installation and operational validation based on design specifications.

5.3 Recommendations

It is recommended that the project proceeds to commissioning and ultimately the operational stage. Some recommendations are made to address certain challenges encountered.

Recommendations pertaining to this study:

- Prior to advancing to the commissioning stage, it is recommended that the conceptual design of the pilot facility and the conceptual design of the Pheroid pressure vessel be audited simultaneously by a regulatory consultant and the HVAC engineer. They can then provide additional input on the overall GMP compliance of the process, equipment and facility as this affords an opportunity to re-work the designs. The heat generated by the pressure vessel during the processing stage should be minimised so that it would not raise the ambient temperature, thereby adversely affecting the stability of the raw materials stored within the facility. Alternatively, the HVAC system would have to compensate for the heat generated by the vessel.

- The facility should be licensed for manufacturing. This involves registering the facility with the South African Pharmacy Council as a manufacturer (this requires establishing a business name under which the facility will operate). The next step is submitting an application for licensing with the South African Medicines Regulatory Authority. This involves an audit for GMP compliance that will assess the facility's suitability for production of investigational products.

- Several requirements have to be met prior to the audit for compliance. These include the establishment of a quality assurance unit and creating the quality assurance policy of the manufacturer. This also involves structuring an organogram of the responsible persons involved in overall quality assurance, quality control, manufacturing and regulation. A site master file is to be completed upon application for licensing. It is necessary to establish the relevant documentation. These include batch manufacturing documents and documentation (procedures) as outlined in chapter 4.

General recommendations:

- The South African Medicines Regulatory Authority should consider doing GMP audits on conceptual facility designs prior to commissioning. Input or guidance from the regulatory authority would be invaluable and may ultimately save time and money.

- The challenges encountered during this study showed that although there is much research done internationally on pharmaceutical technology and engineering, such research within the South African regulatory context should be considered.

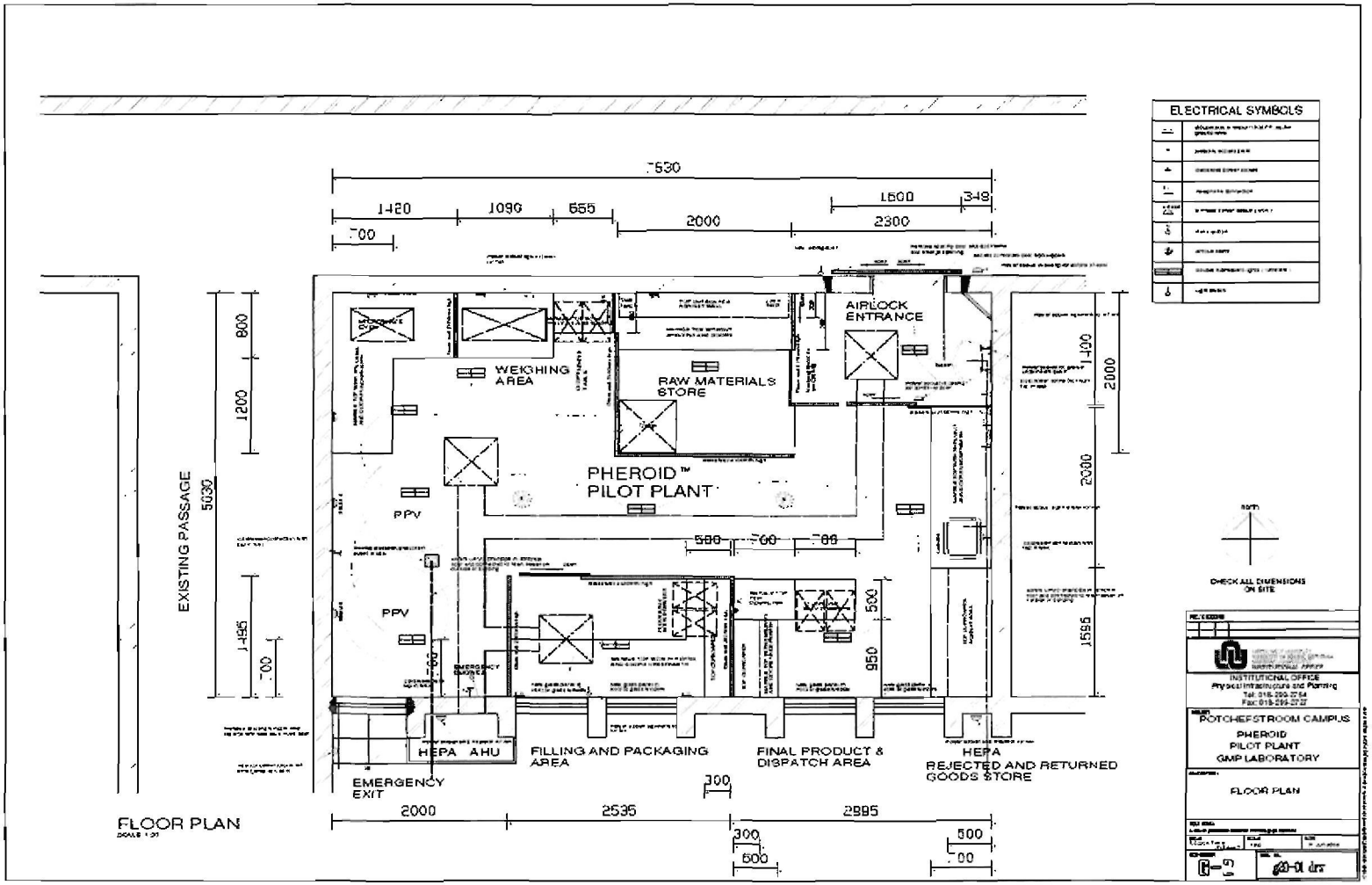


Figure 5.1 Architectural layout of Pheroid pilot plant.

5.4 Conclusion

The introduction to this dissertation highlights a problem that most researchers at academic institutions, who have reached early clinical trial stage of their research, are challenged with. In situations where trial products involve a unique drug delivery system, as is the situation with the Pheroid, opportunities to outsource trial products become limited as sub contractors are not willing to invest in equipment to produce trial product that are at risk of not ever reaching the market. The need to manufacture products using the institutional resources, at minimal costs, and securing research confidentiality has had researchers looking into establishing pilot plants on campuses. This study was done to investigate and propose a design for a GMP compliant pilot facility located within an academic environment, namely the North-West University (Potchefstroom campus).

Chapter 2 explored the Pheroid as a unique drug delivery system that shares characteristics of both microspheres and nano-particles. The Pheroid is a nanosphere formed through a mechanism that differs from both nano-particle and microsphere formation. It is a novel drug delivery system able to transport both hydrophobic and hydrophilic drug substances due to it's a nitrous oxide essential fatty acid (NOEFA) matrix.

Chapter 3 identified the differences between pilot facilities, experimental facilities and commercial facilities. Various policies, guidelines and regulations relating to good manufacturing practices were discussed. Regulatory, product, process, architectural and engineering requirements to be considered in facility design were addressed. A design philosophy that would guide the design process was established.

Chapter 4 includes a discussion on the findings of design evaluation, as well as a series of chronologically modified models. Theoretical requirements (as described in Chapter 3) were applied to design a theoretical model.

It was determined that the allocated facility was not suitable for Pheroid production. A major outcome at this stage of the study was the design of a specialised Pheroid production vessel (PPV). In the normal course of events, with respect to the design of any production facility, the designer would not manipulate process equipment to compensate for facility limitations. However, a suggestion was made by the designer, based on the process requirements and the characteristic behaviour of the Pheroid, to contain several processing steps in a single vessel. The designer therefore outlined the

specifications for the equipment (PPV) so that the process requirements would be met – this made it possible to proceed with the facility design in the allocated space.

A theoretical model was subsequently designed on the premise that the PPV would be designed as prescribed. Shortcomings of the theoretical model were identified through evaluations of its feasibility. The evaluations done revealed the need to obtain input from engineers, architects, contractors, quality control staff and manufacturing staff very early in the process of facility design. If not limited by available space or funds, a facility can be designed purely with process and regulatory requirements in mind.

Three re-worked models are presented in chapter 4, as well as all the revisions that would eventually culminate in the final facility design. The importance of having adequate financial support when undertaking the design of a facility is explained in terms of commissioning and life-cycle cost. It was found that various facets of the design can be manipulated to best achieve the critical process and / or GMP requirements.

Chapter 5 covers the final architectural drawing of the pilot facility, which would be used in commissioning of the pilot facility. When designing a specialised facility such as this, the designer should a) have a sound understanding of the national regulatory requirements; b) be informed of user requirements; c) understand the goals and objectives; d) be familiar with the processes that are to take place within the facility; e) understand the corporate philosophies of the institution or organisation and f) ensure that all the information on processing, including the materials used in production, are provided. Considering the cost and magnitude of such projects, it is imperative that all decisions are made in the design process be well informed. Based on the experience gained in this design process, some recommendations were made to ease commissioning of the facility. Further recommendations were made to encourage more research in this field.

The method used in establishing this pilot facility cannot be standardised, hence it would not be possible to prescribe or devise a stand-alone model for pilot facility design. A few of the challenges unique to this project are:

i. There were some doubts about establishing such a facility within an academic environment, however the participation of the institution and its staff proved to be an invaluable asset;

ii. Limited space and funding necessitated the development of a specialised processing vessel (PPV). More funding was also obtained at a later stage; and

iii. The novelty of the Pheroid drug delivery system and its characteristics were handled with the suitable use of containment and barrier technology.

The aim of designing a Pheroid pilot facility, which would operate within an academic environment, has been achieved (provided that PPV is procured). The final facility design complies with GMP requirements. A full GMP audit will be done after installation of the PPV, and commissioning of the facility.

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Annexure A

FINDINGS OF EMPIRICAL INVESTIGATIONS AND PROCEDURES

A.1 Introduction

The overall aim of the study was to design a Pheroid pilot plant within the academic environment of the NWU. The literature reveals that a pilot facility would have to produce pilot batches that are compliant with cGMP. Although there are no guidelines on establishing a pilot facility, the ideal would be to follow the guidelines for a generic production facility and making the necessary adaptations to produce pilot scale batches that are to be produced as per the Pheroid process requirements. All this has to occur within a facility that would be compliant with current GMP. Thus the investigations were undertaken with the aim of:

i. Establishing the feasibility of a pilot facility at NWU, Potchefstroom campus;

ii. Obtain knowledge of the Pheroid production process and flow of events;

iii. Identification of critical process parameters and critical process equipment;

iv. Determine what the facility design requirements are in terms of user specifications, process requirements and regulation;

v. Investigation of the suitability of the allocated site as a pilot facility

Before an attempt was made to devise or design a model pilot plant, the overall methodology followed was qualitative, hence the selection of the data collecting tools varied based on the most suitable strategy for gathering the necessary information. These are described together with their intended purpose in each of the investigations followed. The factors identified in literature study on Pheroid production, facility design, regulatory and GMP requirements will be used to guide the investigational process.

A.2 Investigation on feasibility

A.2.1 Objectives and findings on feasibility

The objective of this investigation was

i. to establish whether the institution (NWU) was supportive of a Pheroid pilot facility on campus,

ii. if the facility would affect the health and safety of the staff, students and the environment,

iii. to identify the adequacy of resources for the project. The findings are tabulated in Table A.1.

Table A.1 Investigation on feasibility of a Pheroid pilot plant at NWU Potchefstroom campus.

Method of Investigation:	Interview of Pheroid pilot plant project managers	
Persons interviewed	Prof. A.F. Kotze and Ms Anne Grobler	
Date: 19/06/2006	Time:11:00 -13:00	Venue: NWU (Potchefstroom)
Investigation	Findings	Positive / Negative / Neutral
Institutional requirements		
Corporate Philosophy	Further research and development.	Positive
Institutional Policy	Supportive of establishment of a pilot plant for furthering developments in Pheroid technology on condition that the safety of students, staff and environment are priorities of the institution.	Positive
Environmental Feasibility	There are no by products of Pheroid manufacturing that would be released into the environmental air or drainage systems as the basic components of the Pheroid are essential fatty acids, water and nitrous oxide which are not classified as harmful to the environment. The active drug substance particulates would be contained within the facility as per the user requirement.	Positive
Municipality	The NWU is designated research area and does not present a threat to community.	Positive
Resources		
Human resources		
Personnel	Project management staff, research scientists, postgraduate students and support staff constitute personnel.	Positive

Table A.1 Investigation on feasibility of a Pheroid pilot plant at NWU Potchefstroom campus (continued).

Expertise	Personnel engaged in the facility are experts in their fields and are the most knowledgeable about Pheroid technology.	Positive
Training	Ongoing training of personnel takes place within the unit.	Positive
Financial resources	Limited budget at the time of interview. Project management are in the process of inviting investors to fund the project. The finances required at this stage of the project was not known.	Impact unknown
Premises		
New Building	No	Neutral
Renovation of existing site	Location on NWU campus.	Positive
	Available. An existing laboratory of dimensions 7,55 m X 5,04 m. The size of the facility is small.	Neutral. Subject to what the process requirements are.
Nature of the facility	Produce pilot scale batches for investigational / trial product. Products produced are oral liquid and topical dosage forms.	Neutral: Subject to process requirements and product characteristics.
Instrumentation		
Confocal laser scanning microscope	Available within the Phertec unit.	Positive
Zeta potentiometer	Available within the unit.	Positive
Analytical laboratory services	Have access to an analytical laboratory for quality control. The analytical laboratory is existent and not part of the Pheroid pilot facility.	Positive

A.2.2 Conclusion on Feasibility

The feasibility in terms of the institutional requests are favourable, the NWU in support of progress in this field of research has allocated a site for the establishment of the pilot plant on campus. The feasibility on human resources and instrumentation for quality control are also positive. The available finances and the size of the facility may influence the feasibility of the project. These would be re-evaluated upon establishing what the user and process requirements are.

A.3 Investigation of Pheroid production process

The approval to establish a dedicated Pheroid pilot production facility implied investigating the requirements of the Pheroid production process.
This investigational procedure / strategy involved the data collecting techniques of interview; observation and document review / scan.

A.3.1 Objective and findings of Pheroid production process

The relevance of this investigation to the aim of the study is the identification of factors in the production process that are important for product quality as these factors may have an influence on the design of the facility. The objectives of this investigation were:

i. to establish the process requirements;

ii. to establish the critical process parameters;

iii. to establish to what extent GMP has been followed in experimental batch production / product development.

The findings are tabulated in Table A.2; A.3 and Figures A.1, A.2 and A.3.

Table A.2 Pheroid and pro-Pheroid process description.

Method of Investigation	Interview and observation	
Person/s interviewed	Mr Dale Elgar (Research scientist. : Pheroid production for experimental purposes).	
Date: 20/06/2006	Time: 09:00- 16:00	Venue: Room 110, School of Pharmaceutics
Process description		
ENQUIRY	FINDINGS	
Major Process steps	Pheroid: Step 1-Gassing water with N_2O under pressure for period of four days. Step 2-Heating to approx 70-75°C. Step 3-Weighing, heating and cooling of oil phase. Step 4-Addition of oil phase to gassed aqueous phase. Step 5- Homogenise. Step 6- Test for Pheroid formation. Step 7*-Addition of API. * Addition of API can take place at step 2 and is dependant on the solubility of the API.	
	Pro-Pheroid (No aqueous phase). Step 1-Weigh and heat oils. Step 2-Add API. Step 3- Homogenise. Step 4-Gas under pressure with N_2O for four days.	
Block diagrams	See Figure A.1 (same as Figure 4.5 in chapter 4)	
Process flow diagrams	See Figure A.2 (Pheroid) and Figure A.3 (pro-Pheroid)	
Utilities (WFI, DI water, CIP)	Process water used is USP grade obtained from RIIP. Water used for cleaning: Potable water. Gas supply ports connected to pressure vessel from gas cylinder.	

Table A.2 Pheroid and pro-Pheroid process description (continued).

Major support equipment	-Fridge. -Surface agitator/shaker.
Major process equipment	-Weighing equipment. -Pressure vessel (10 litre vessel used for gassing under pressure) and gas cylinder. -Heating plate, microwave heating for oil phase up to 130°C. -Homogeniser that can reach the range of (13 000 to 14 000 rpm).
Facility Description (Experimental facility/laboratory)	
Equipment layout / arrangement	The site of the experimental laboratory is approximately 2.0 m x 3.0 m with one window, the work surface extends from one end to other holding all the equipment used, except for the scale which is on a separate work surface on the opposite side. A sink is present with access to potable water for cleaning glassware. Cupboards below the work surface are used for storage of glassware and a cupboard is dedicated for holding/storage of files, records etc.
Personnel / material / component flow	Due to the layout of the experimental facility, the weighing of raw materials occur on one side of the laboratory while the heating, cooling and homogenisation occurs on the opposite side. The personnel flow is restricted to only the Pheroid manufacturer. There are no specifically dedicated component areas in the experimental laboratory.
Controlled environments	Access into the experimental laboratory is controlled to the manufacturer and student assistant. No specific containment processes observed nor controlled manufacturing environment with the exception of the temperature monitoring.
Materials of construction	Glass windows, melamine bench surface, painted walls and tiled floor.

Table A.3 Findings on procedures at experimental laboratory.

Method of Investigation	Interview, observation and document viewing.	
Person Interviewed	Mr Dale Elgar (Research scientist: Pheroid production for experimental purposes).	
Date: 20/06/2006	Time: 09:00-16:00	Venue: Room 110, School of Pharmaceutics
Procedure Enquiry	**Addressed (Y/N/ Partially)**	**Method**
Raw material receiving area	Yes	No procedure, logs kept. No defined receiving area.
Raw material sampling	Partially	Done , no procedures in place.
Raw material storage	Yes	No procedure in place.
Raw material vendors	Partially	No approved vendor lists and no contracts.
Weighing area	Yes	No operating manual or service records.
Batch manufacturing documents / records	Partially	File records of all experimental batches.
Mixing area	No	Area undefined.
Bulk final product sampling and storage	Partially	Procedure perhaps not well-documented but in place: 1 ml of Pheroid formulation is transferred to microfuge tubes for each of the analytical tests. Dilutions for each analytical procedure well described.
Analytical testing lab (QC)	Partially	CLSM and zeta potential done in house, other analytical test done by NWU Pharmaceutical Chemistry Analytical Unit. No formal contract.

Table A.3 Findings on procedures at experimental laboratory (continued).

Packaging and labelling Process	Partially	Process not defined. Pheroid is filled into amber glass bottles with name of product, batch no and date.
Goods reject area	No	No provision made.
Goods destruction procedures	No	Destruction of batches is by disposing the Pheroid base into sink. No procedure.
Retention sample store	No	No retention samples of each batch produced. However stability samples retained.
Temperature control	Yes	Temperature log, no procedure in place.
Specialised ventilation or air handling system	Yes	Extraction fume cupboard, no procedures for when used.
Equipment procedures	Partially	Pressure vessel, weighing device, microwave oven, however maintenance and operating procedures non existent.
Cleaning procedures	Partially	Cleaning takes place, no procedures and cleaners are not informed of how to handle or clean various equipment.

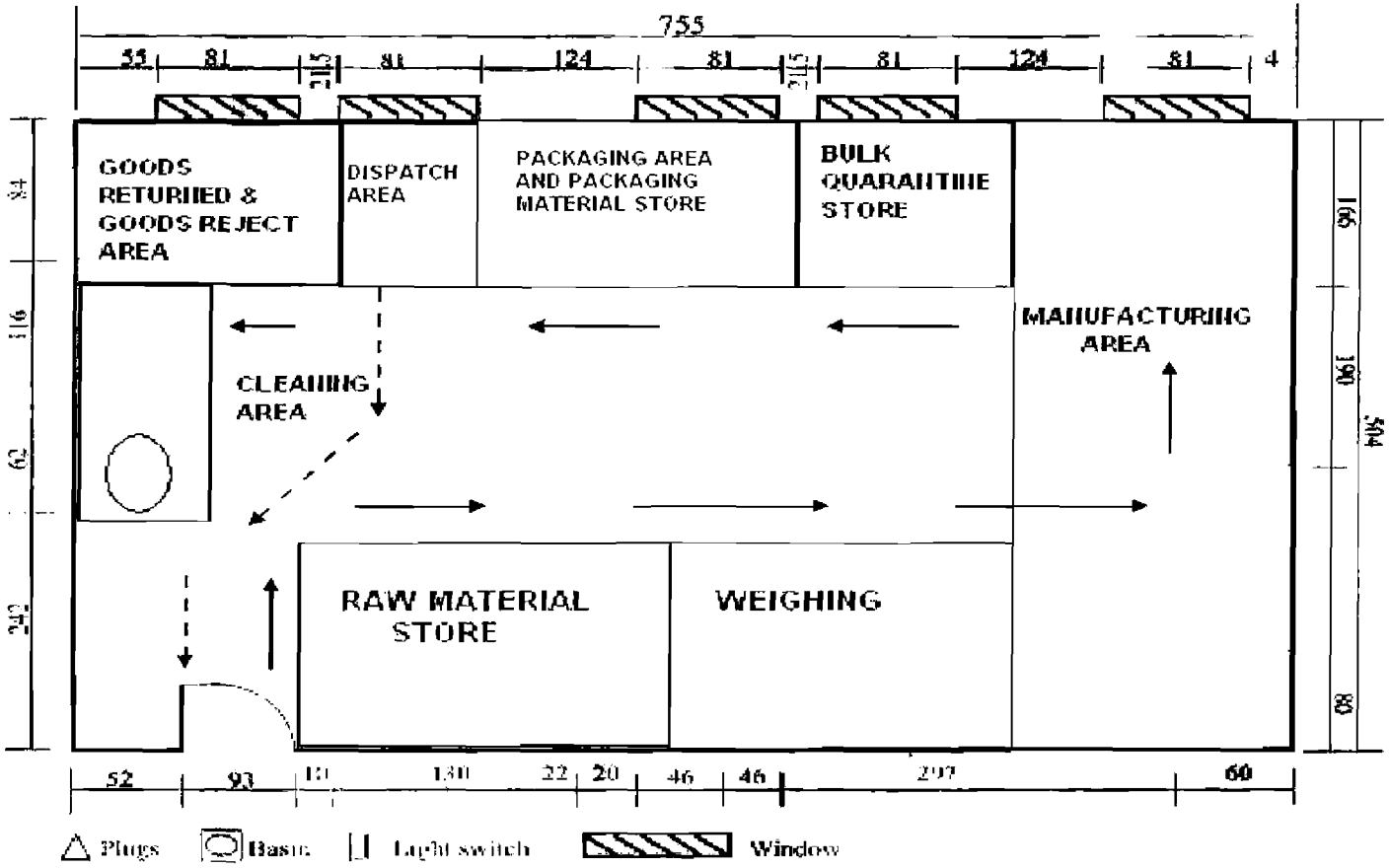


Figure A.1 Box representation of facility layout and process flow as per GMP.

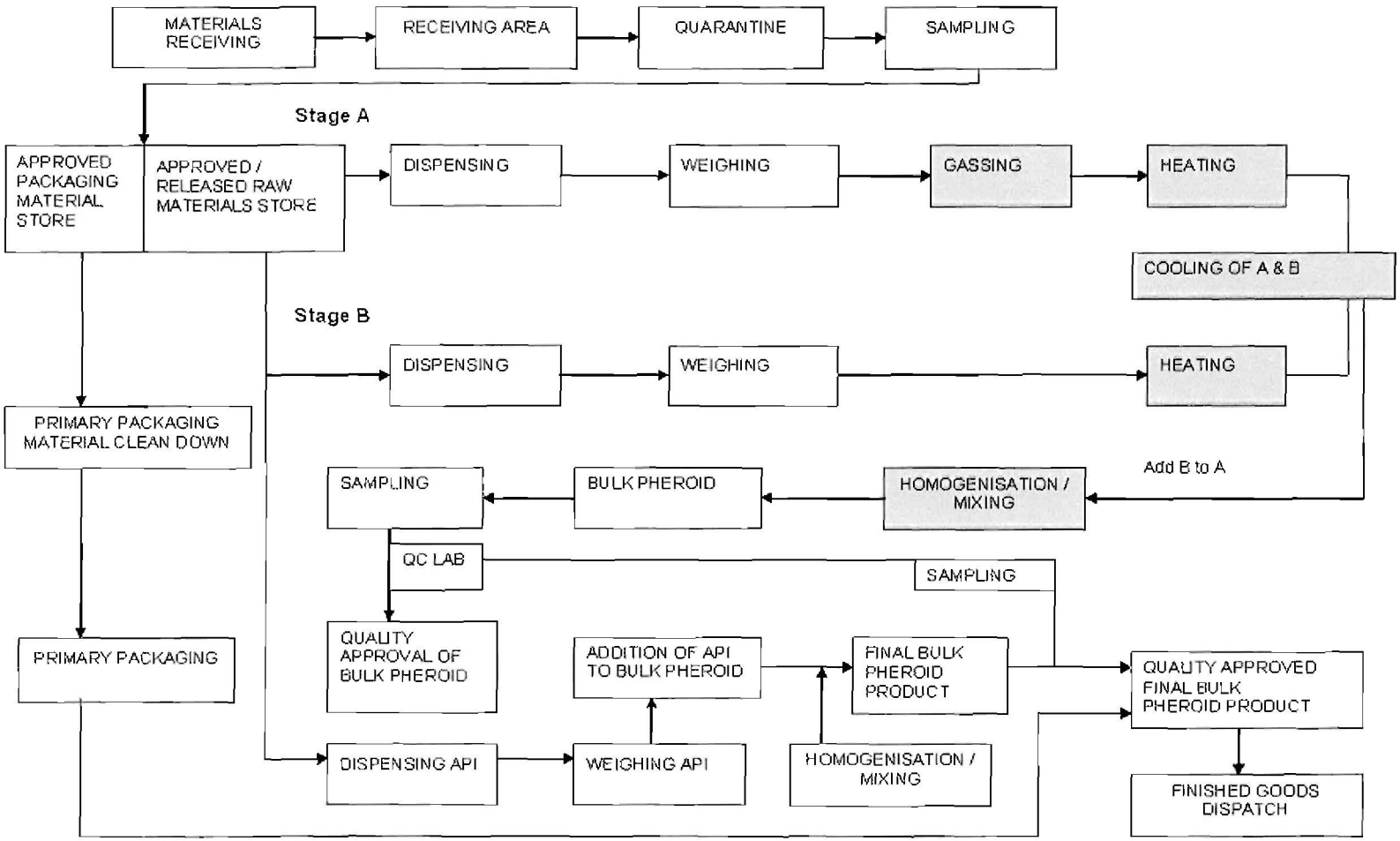


Figure A.2 Process flow of Pheroid production.

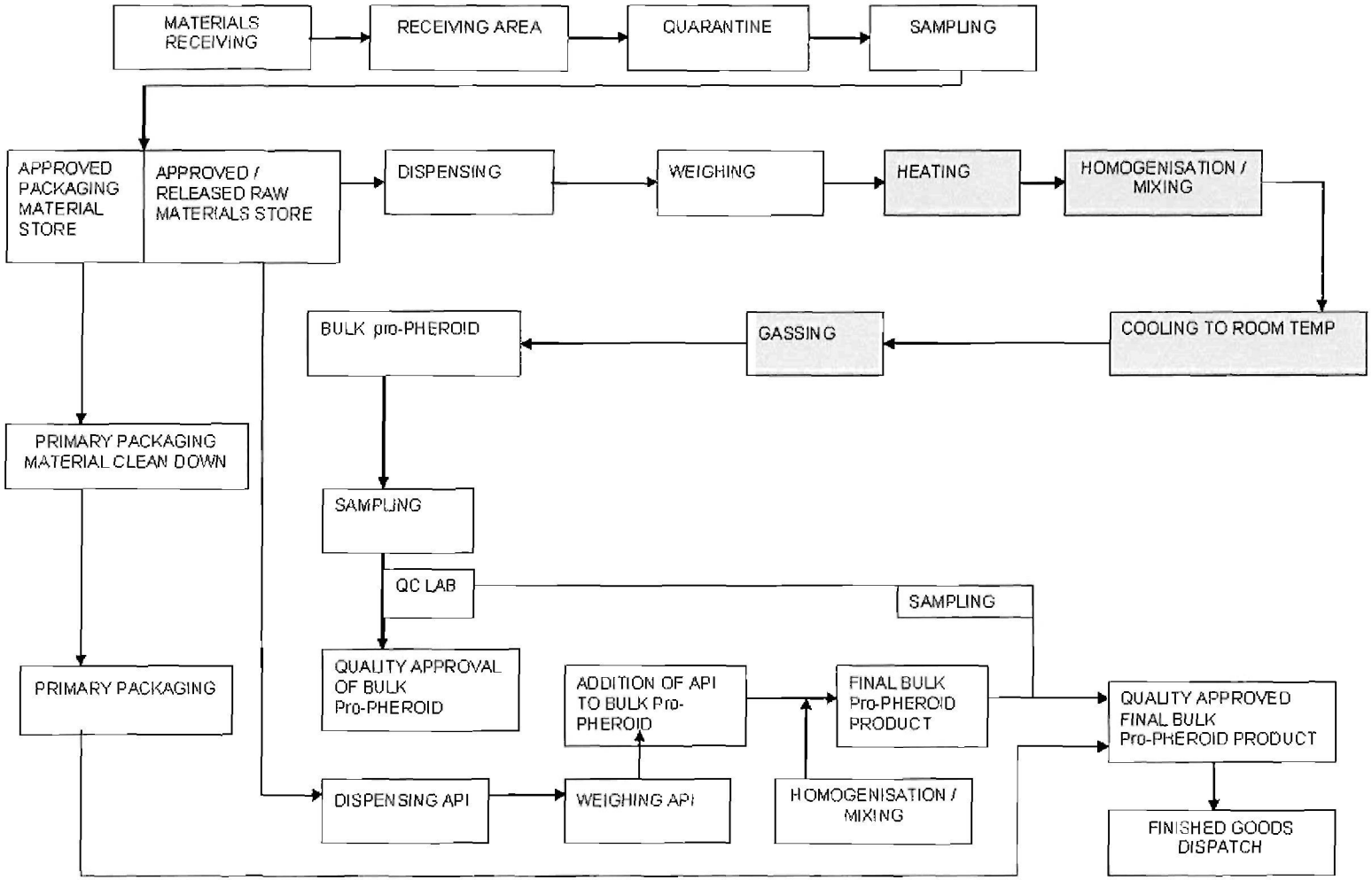


Figure A.3 Process flow of pro-Pheroid production.

A.3.2 Conclusion on Pheroid process requirements

The findings reveal that whilst records in the form of experimental production batches, temperature logs and materials logs were kept, there was inadequate documentation in place defining the relevant procedures. The Pheroid and pro-Pheroid produced were done on diarised requests and did not have a requisition for manufacture and hence traceability of these batches could not be verified. There were no defined areas of materials receipt, dispatch or transfer records. The findings in Table A.3 further emphasises the poor implementation of GMP and would require devising procedures to govern operations and ensure repeatability of processes used. The available space in the experimental lab was in fact insufficient to have defined areas of operations. The relevance of investigating the experimental laboratory is that it would provide an awareness of the current use of GMP in the processing and the likelihood of possible factors that are facility related that would affect processing on a larger scale.

A.4 Investigation of design requirements

The investigation of the design requirements are done on establishing specifically defined user requirements, product characteristics and regulatory requirements. These are obtained through inquiry from the manufacturer and regulatory requirements are determined from existing GMP of the experimental facility and literature.

A.4.1 Objectives and findings on facility design requirements

The objectives of this investigation are to:

i. establish if there are any specific user / manufacturer requirements to be considered in facility design;

ii. establish if the product characteristics require specific design considerations;

iii. establish if individual processing steps or individual ingredients require specific safety handling and ultimately design considerations.

The findings on facility design requirements are tabulated in Table A.4; A.5; A.6 and A.7.

Table A.4 Findings on specific user requirements.

Method of Investigation	Interview	
Persons interviewed	Ms Anne Grobler	
Date: 18/06/2006	Time: 09:00 - 11:00	Venue: Room 110, School of Pharmaceutics
Manufacturer / user requirements		
ENQUIRY	FINDINGS	
Regulatory	That the Pheroid pilot facility be designed such that the facility meet with the national regulatory requirements.	
Confidentiality	Pheroid is a novel drug delivery system that has been patented. A confidentiality agreement was signed. Details of formulation and production are hence not to be disclosed. Critical parameters can be identified for the purposes of facility design.	
	The classified nature of the Pheroid technology therefore would limit information disclosed in this project. These would however be built into the requirements for the facility.	
GMP concerns		
Product protection	The characteristic of Pheroid as a drug delivery system involves its ability to entrap molecules (API's) and similarly is able to entrap particulates. Hence to ensure that the quality of the product is not compromised, it should be ensured that the product is produced within a desired level of protection against possible particulate contamination.	
Non-GMP concerns		
Protection against organism resistance	This concern of the user stems from the use of known active drug substances used in the formulations. These agents includes anti-malarial, anti-tuberculosis and anti-retroviral agents. The user therefore recommends that the design of the facility limits particulate movement out of the facility and reduce operator exposure to these substances.	
Cost containment	The availability of limited funds has resulted in the user requesting only essential changes be made.	

Table A.5 Findings on product description and characteristics.

Method of Investigation	Document observation
Dates: Period 01/07/2006-14/07/2006	Venue: Experimental Laboratory room 110 in building G16
Product description	
Enquiry	Findings
Product type(s)	The product are of two types which are the Pheroid and pro-Pheroid. These would form the drug delivery base for the final product. The final product produced would include the active drug substance entrapped in the Pheroid or dissolved in the pro-Pheroid. The product (Pheroid / pro-Pheroid base) are liquid.
Dosage form	The formulations intended for manufacture in the pilot facility are liquid oral dosages (suspensions / emulsions) and may include topical dosage forms such as lotions.
Volumes (optional)	The current experimental batch manufacturing occurs on campaign basis and the same will apply for the pilot facility due to the long gassing periods. Hence the facility would not be designed for increased throughput of product.
Batch size (s)	The batches produced at experimental level have been no greater than five litres and as small as 100 ml. The intended volume for the pilot facility is approximated a maximum of 100 litres.
Formulation (optional)	The exact formulation is classified and hence would not be revealed. The process of manufacturing has been reviewed and only the deemed critical steps have been recorded for purposes of establishing the critical process requirements for consideration in the design of the facility.
Package (s)	Currently volumes of 100, 250 ml and 500 ml have been filled in the experimental laboratory. It is envisaged that the same volumes would apply for the pilot facility. These are subject to clinical trial protocol requirements.

Table A.5 Findings on product description and characteristics (continued).

Product features (physical characteristic)	The product produced are characteristically liquid with varying densities dependant on the formulation and the characteristic solubility's of the API. The Pheroid has the ability to entrap particulates once formed, this characteristic enables it to be an effective drug delivery system but also presents a challenge in that contaminants and other unwanted particulates can become entrapped if exposed to the Pheroid. Hence there is a need to consider closed processing or barrier technology to avoid unwanted particulates being entrapped in Pheroid.
Solubility	The Pheroid base is often used for more water soluble API's and the pro-Pheroid base for the more oil soluble API's. See Table A.6 and A.7 for individual ingredient solubility.
Heat, light, air sensitivity	The Pheroid base is sensitive to high temperature and this may interfere with the quality of the Pheroid formed. See Table A.6 and A.7 for individual ingredient sensitivities.
Stability	The stability of the Pheroid is influenced by the way it if formulated. Stability is still being investigated with various Pheroid formulations.
Safety and Handling	Safety aspects in gassing, heating and transferring of process and in-process materials are critical. In the case of the scaled up pilot scale manufacturing as opposed to the experimental scale, the risks of handling larger volumes of heated product may present as occupational hazards in the pilot facility. See Table A.6 and A.7 for individual ingredient safety requirements.
Raw materials, reactants, intermediates, processing aids	Table A.6 and A.7 provides more data on individual ingredient characteristics.

Table A.6 Characteristics of components of Pheroid base (adapted from product material safety data sheets (MSDS)).

	N_2O	Polyethylene Glycol 400	Cremaphor RH40	Vitamin E	Vitamin F ethyl ester
TOXICITY/ POTENCY	No known effects on carcinogenicity or mutagenicity. Heavy occupational exposure have resulted in myeloneuropathy.	Non toxic and non irritant. WHO set limit of 10mg/kg body weight.	May alter absorption of active substances. Anaphylaxis reported on parenteral administration.	Tocopherols are well toleratedin large oral doses.	Non toxic. Plant derived. Easily biodegradable.
PHYSICAL PROPERTY	Colourless sweet tasting and sweet smelling gas.	Clear colourless to slightly yellow, viscous liquid. Have a characteristic odour, bitter and slightly burning taste.	White to yellowish, almost odourless.	Practically odourless, clear. Colourless to yellowish viscous oil.	Pale yellowoily liquid with characteristic odour.
HYGROSCOPICITY	Not applicable.	Not found.	Not found.	Not found.	Not found.
SOLUBILITY	Not found.	Water soluble. Enhances aqueous solubility.	Forms clear solutions in water solubility > 490 g/l, ethanol, chloroform,toluene and xylene.	Practically insoluble in water. Freely soluble in acetone, ethanol,ether and vegetable oils.	Soluble in oils and fats.
LIGHT, AIR, HEAT, SENSITIVITY	All gas cylinders must be regarded as pressure vessels and stored appropriately. Never expose to high heat.	Stable in air and in solution.	Solutions become cloudy as temp increases. Protect from light.	Should be stored under inert gas in an airtight container in a cool dry place protected from light.	No data available.
SENSITISATION	No known effect on skin or eye.	Non irritant.	Cosmetic and present no hazards.	Unlikely to cause or pose any hazard to human health.	Sensitivity test on guinea pigs/DGF method reveals non sensitising.
SAFETY ASPECTS	Safety goggles, gloves and shoes should be worn when handling vessels.	Eye protection is recommended when handling.	Non hazardous to environment or man.	Handle with gloves and eye protection.	Non hazardous. Used as cosmetic, no negative effects reported.

Table A.7 Characteristics of active pharmaceutical ingredients (APIs) used in Pheroid formulations (adapted from MSDS of USP convention, 2007).

	ETHAMBUTOL HYDROCHLORIDE	ISONIAZID	LAMIVUDINE	MEFLOQUIN HYDROCHLORIDE	RIFAMPICIN
TOXICITY/ POTENCY	No carcinogenicity from tests on mice were observed. Oral rats: LD50: 6800 mg/kg. Oral Mouse: LD50: 8900 mg/kg.	Emits toxic fumes under fire conditions Oral rats: LD50: 1250 mg/kg. Oral mouse:LD50: 133 mg/kg.	Oral rat: LD50: >2000 mg/kg. Oral mouse: LD50: not found. Studies in mice and rats have shown no evidence of carcinogenicity.	Oral rat: LD50: 880 mg/kg. Oral mouse: LD50: 810 mg/kg.	Non carcinogenic. Increased incidence of hematomas in female rats. Oral rats: LD%): 1570 mg/kg. Oral mouse:LD50: 500 mg/kg.
PHYSICAL PROPERTY	White crystalline powder, odourless.	Colourless or white crystals or crystalline powder, odourless.	White to off white crystalline powder.	White to white crystalline powder, odourless.	Reddish-brown crystalline powder, odourless.
HYGROSCOPICITY	Hygroscopic. Avoid exposure to moisture.	Hygroscopic. Avoid exposure to moisture.	Not found.	Not found.	Hygroscopic. Avoid exposure to moisture
SOLUBILITY	Freely soluble in water. Soluble in alcohol and methanol.	Freely soluble in water. Sparingly soluble in alcohol. Slightly soluble in chloroform.	Water soluble. Sparingly soluble in methanol, slightly soluble in ethanol.	Slightly soluble in water. Soluble in ethanol and ethyl acetate.	Very slightly soluble in water.
LIGHT SENSITIVITY	Store in tight container.	Avoid exposure to light and air.	Store in tight, light resistant container. Avoid exposure to light and heat.	Not found.	Avoid exposure to light, heat, air and oxygen.
SENSITISATION	Hypersensitivity, optic neuritis, impaired kidney function aggravated on exposure.	Irritancy data reveal that moderate irritation can be expected.	Inhalation may cause irritation. Exposure may cause eye and skin irritation.	Rabbit/eye irritancy data reveal that an irritant	No special ventilation requirements. Irritation to eye and skin. Hypersensitivity aggravated on exposure.
SAFETY ASPECTS	Use gloves, protect exposed skin. An approved dust mask must be used.	Avoid contact, use gloves, glasses and protect exposed skin.	Avoid inhalation and contact. Use safety goggles and protective clothes.	Avoid contact, use gloves, glasses and protect exposed skin.	Use gloves, protect exposed skin. An approved dust mask.

A.4.2 Conclusion from findings on facility design requirements

It is evident that the Pheroid is a unique system that requires sufficient protection against particulate contamination. The user requirement to act against the possibility of drug resistance by containing the particulates to remain within the facility indicates that a system of containment or isolated processing be considered. The light sensitivity of some of the actives require specialised handling. The characteristic nature of ingredients used reveal no hazardous or toxic materials are used, however some ingredients are sensitive to light, air, heat and moisture which would affect the storage requirements for these raw materials.

A.5 Investigation of the allocated site

The investigation of the allocated site was to provide information on the suitability of the site based on the product, processing user and GMP requirements. It also involves assessing the usability of existing materials within the site and the probability of retaining as much of the utilities and electrical components in the original locations as per the user request to limit unwanted costs.

A.5.1 Objectives and findings on the allocated site

The method of data collection included: interview, observation, document / map collection and photographs of the site. The objectives of this investigation were:

i. to establish the suitability of the site as a pilot production facility;

ii. to establish whether the site is suitable to Pheroid production;

iii. to determine the necessary changes that has to be made to the site to make it a cGMP production facility (minimize the risk of contamination and cross-contamination).

The findings on this investigation are tabulated in Table A.8; Figures A.4; A.5; A.6 and pictures in Figures A.7 to A.18.

Table A.8 Findings on allocated site.

Method of Investigation:	Interview, observation, document collection and photographs	
Persons interviewed	Ms Anne Grobler and Ms Elza Moorcroft	
Date: 21-24/06/2006	Time:08:00-16:00	Venue: NWU (Potchefstroom), G2 ground floor room G20
Investigation	**Findings**	
	Site	
Location	The allocated laboratory G20 is located in building G2 (Pharmaceutics building) on NWU, Potchefstroom campus.	
Size	The allocated site is a laboratory of 7,55 m x 5,04 m in dimension.	
Access for further investigation	Prof. A. F. Kotze has given permission to access the site for purposes of investigation on 21/06/2006.	
Location relative to campus surrounding and adjacent buildings.	This building is identified as building G2 on the campus map. Figure A.5 indicates the location of the building on the campus map. The building is adjacent on the left to a cluster building identified as G3 and G4 (also known as the Spider building) which houses the Natural Science library. G2 is separated by approximately 20 metres of lawn from the library. G2 is attached to G20 on the right. There is an interconnecting walkway that connects the two building on the first floor of G2. The front and rear ends of the G2 building are parking areas for staff and students.	
Location relative to floor and adjacent offices.	Units G09 to G16 are offices of staff of the department of Pharmaceutics. G01 and G02 on the left of the corridor are the male and female rest facilities (toilets). Unit G03 is the hazardous materials store. There are a total of four laboratories on the ground floor including the allocated site; the others namely; G19; G18 and G17 are post graduate research laboratories. Figure A.4 is a floor plan of the location of the allocated site which provides clarity on the location of the site relative to other offices and laboratories on that floor. Unit G05, G06 and G07 are combined into a single Pharmaceutics experimental laboratory.	

Table A.8 Findings on allocated site (continued).

Current internal layout of allocated site.	The internal layout and dimensions of the laboratory are reflected in Figure A.6. Pictures (Figures A.7 to A.18) taken by an Olympus Digital 2 mega pixel camera reveal the internal layout. The various sections of the allocated site including the ceiling and floor finishes were photographed for purposes of identifying the materials used, existing utility systems and the containment ability of the site as is.
Location of passages and walkways around allocated site.	The laboratory is adjacent to a corridor on the left that leads to the entrance of the building. These can be observed from Figure A on the layout of the ground floor of G2 that houses the allocated site G20.
Structural features of allocated site	
Building Structure	The building G2 that houses room G20 (allocated site for the facility) is a four storey concrete, iron and brick structure. The observations recorded below have also been captured by camera and can be observed in pictorial form in Figures A.7 to A.18.
Floors	The unit was recently tiled and has a rough top surface. The spaces between the tiles are filled with grout.
Walls	The walls are concrete and brick and are neatly painted.
Ceiling	The ceiling board seems to have been added below the concrete slab. A noticeable gap between the window and wall surface exists. The ceiling panels are inserted so that ridges are visible. This is however neatly painted.
Windows	The site has five large windows each of which has two frames. The upper frame has glass of rough surfacing facing the interior, which is a sealed frame (i.e. it cannot be opened). The lower frame is fitted with smooth glass and is the larger of the frames, and is able to open. All the windows are on the same side of the room.

Table A.8 Findings on allocated site (continued).

Fixed furniture / structures	The horizontal structures are mainly work surfaces, cupboards and racks made from wood with melamine covering with the exception of the sink and weighing table. The weighing surface is a marble top and concrete support panels.
Doors	The door is a standard lockable wooden lever door. An emergency switch is visible and may indicate a security access control mechanism.
Utilities	The basin is deep (granite) and drains into a ground drainage system. The basin has two taps (hot and cold water). Hot water is produced through a mini heating unit at the base of the basin.
Electrical	The plugs (power sources/points) are standard RSA 3 pin plug points, the electricity cables for these run along the wall surface and is visible although painted. The lighting within the unit comprises of eleven fluorescent banisters that run parallel in two rows. The banisters are fitted onto the surface of the ceiling.
Other	A wooden bulletin board and whiteboard is attached to the wall. Safety issues such as fire hose and extinguisher as well as evacuation procedures are observed.

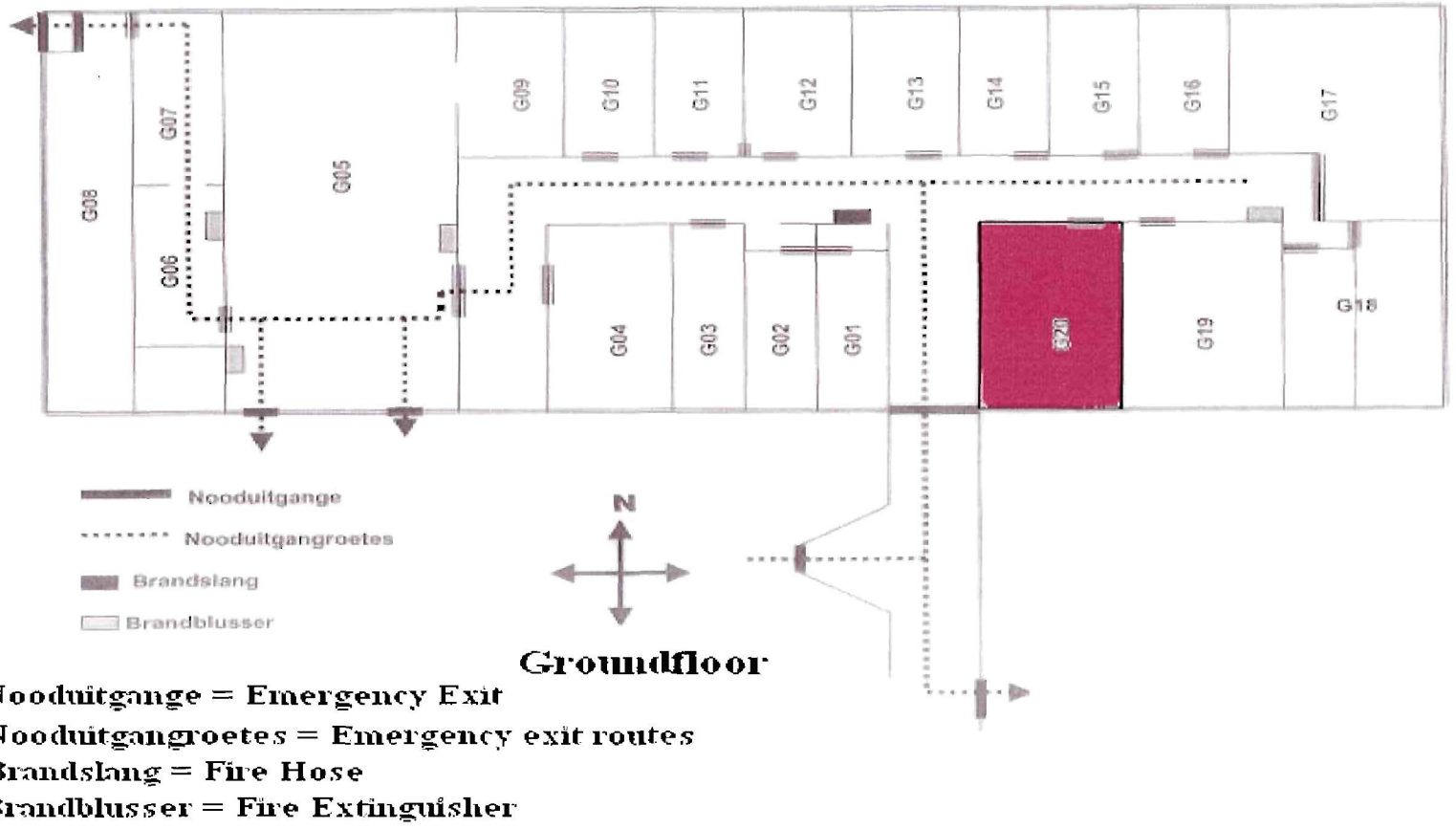


Figure A.4 Floor plan of Allocated Site (G20).

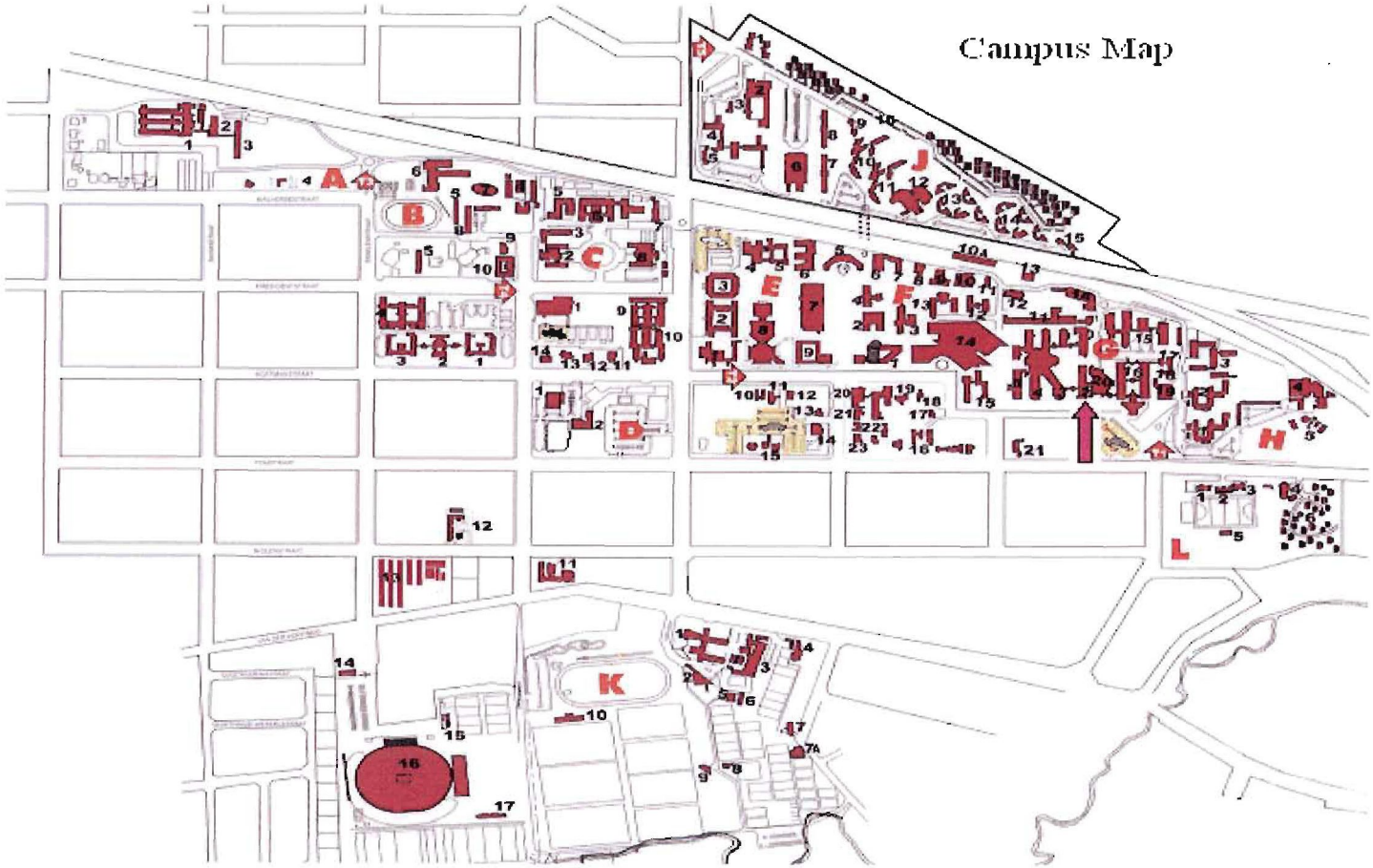


Figure A.5 Campus Map (G2 indicated by pink arrow).

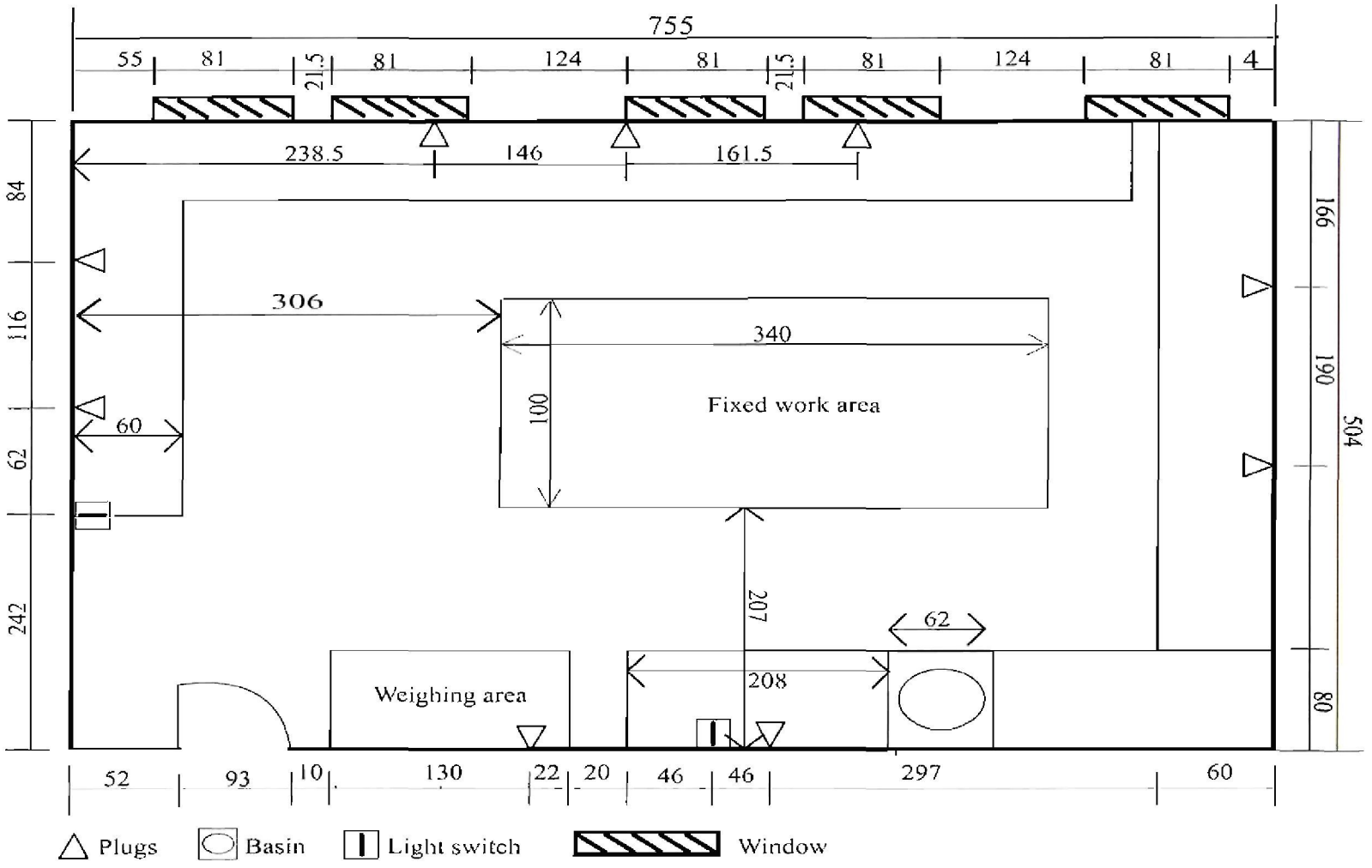


Figure A.6 Internal layout of allocated site.

Photographs of the existing structural components of the allocated site (Figures A.7 to A.18).

Figure A.7 Entrance of Allocated Site.
This picture depicts the entrance area of allocated site as at 21/06/2006.

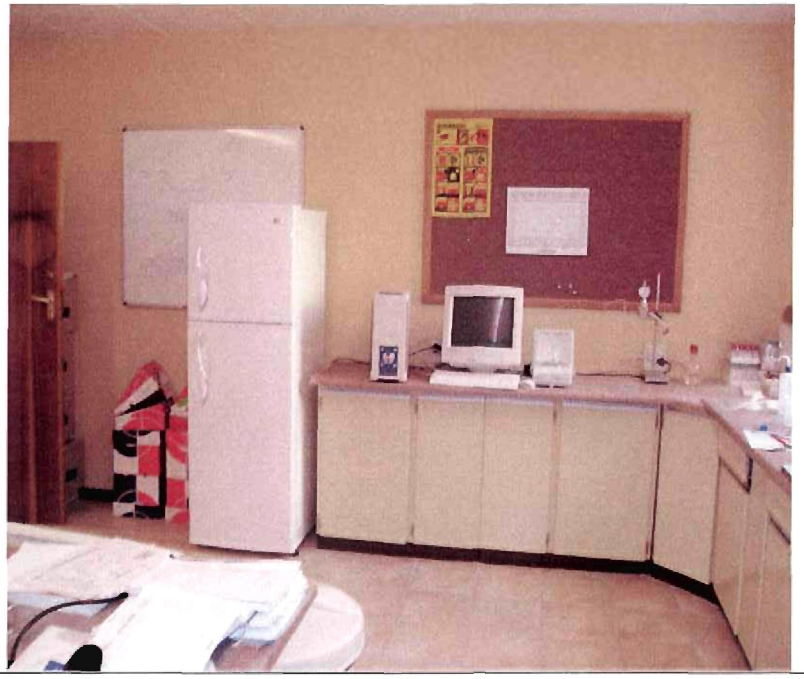


Figure A.8 Left layout of facility.
Picture depicts the wall and fittings along entrance side from left to right. Dimensions from entrance door to wall on right is: 5.04 m.

Figure A.9 Layout from left corner to central opposite.
Picture continuation from left to right along length of room.

Figure A.10 Layout from central to right opposite.
Picture continuation along length from previous picture.

Figure A.11 Layout of central workspace.
Picture of central workstation.

Figure A.12 Layout left to right central view.
Picture depicts front to back view of laboratory from entrance side.

Figure A.13 Layout on right of entrance.
Picture depicts opposite end from left to right along the wall, including solid weighing station on extreme right hand side.

Figure A.14 Layout of window relative to ceiling.
The ceiling, window and wall closure reflecting that ceiling is sunken allowing for a gap between the window ceiling and wall.

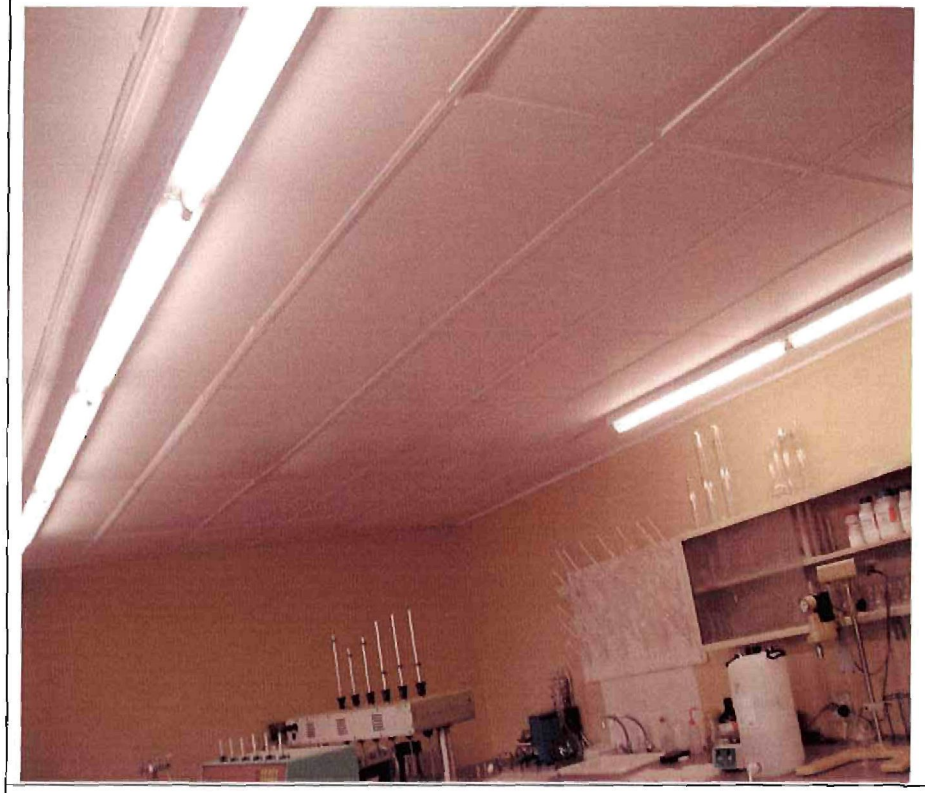


Figure A.15 Layout of lighting along ceiling.
Picture depicting ceiling and light fittings.

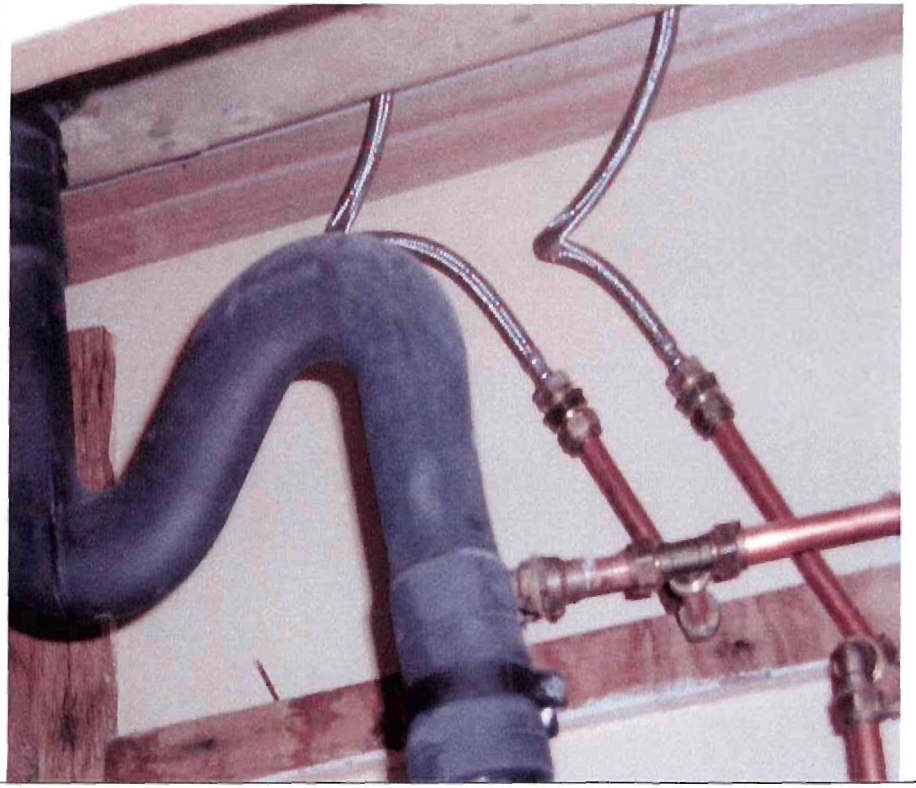


Figure A.16 Water utility drainage.
Drainage and water source system.

Figure A.17 Water utility supply at sink.
Sink fitted in laboratory.

Figure A.18 View of facility relative to adjacent corridor.
Angled outer view of laboratory/site opposite the door entrance.

A.5.2 Conclusion from findings on the allocated site

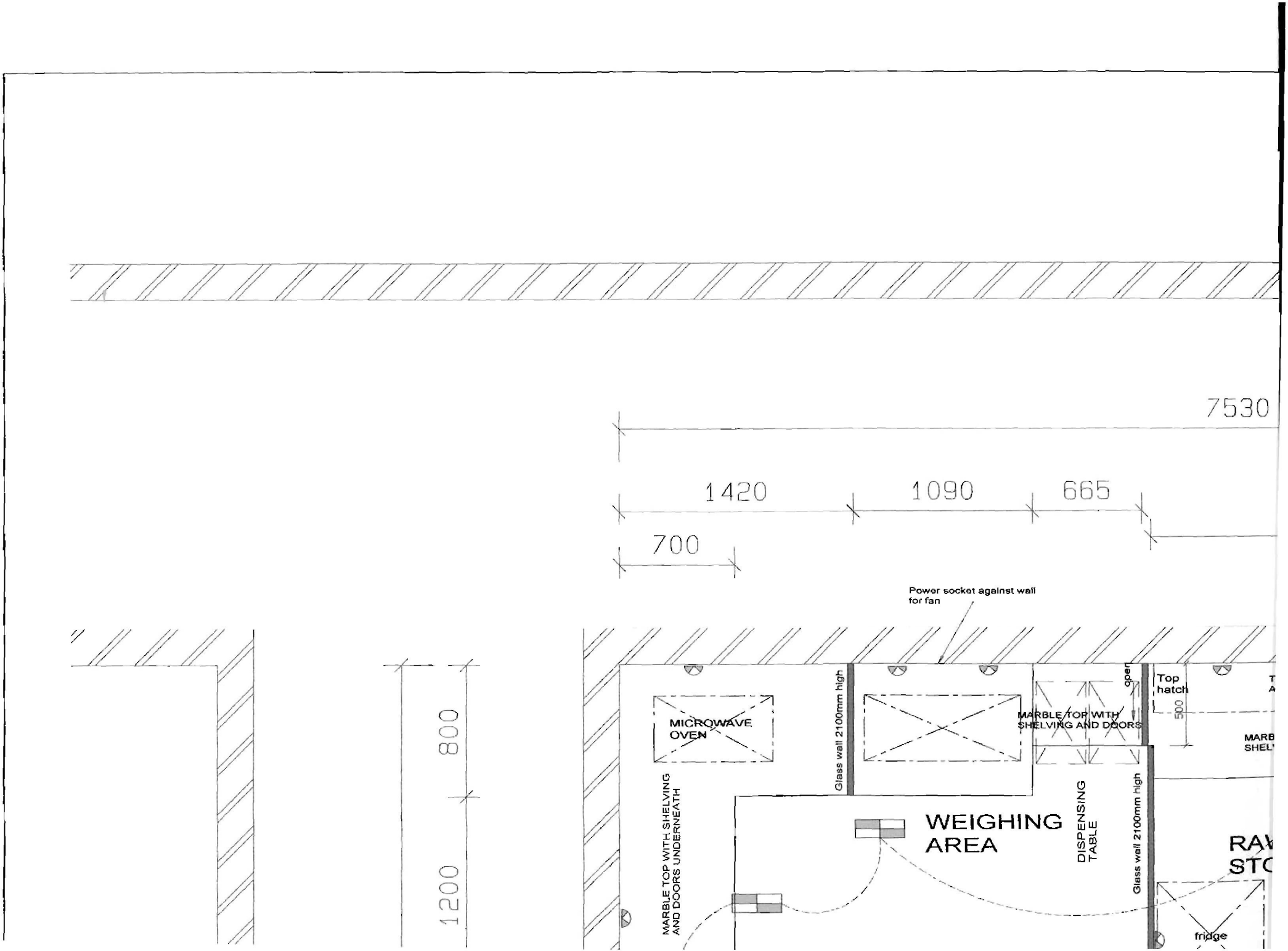
The allocated site reveals that the site in terms of location does not present a threat to the staff, student or environmental safety. The site allocated may be however too small to house the necessary steps in Pheroid manufacture. The current materials of the floor, ceiling and window does present a challenge with respect to potential contamination. The materials for the ceiling floor and wall paint would have to change. The utilities does imply flow pattern problems which can be remedied with effective documentation and procedures. The layout of the required component areas as per the personnel, materials, product, air and waste flow patterns would further incur added risks of not achieving GMP due to the process requirements and size of the facility.

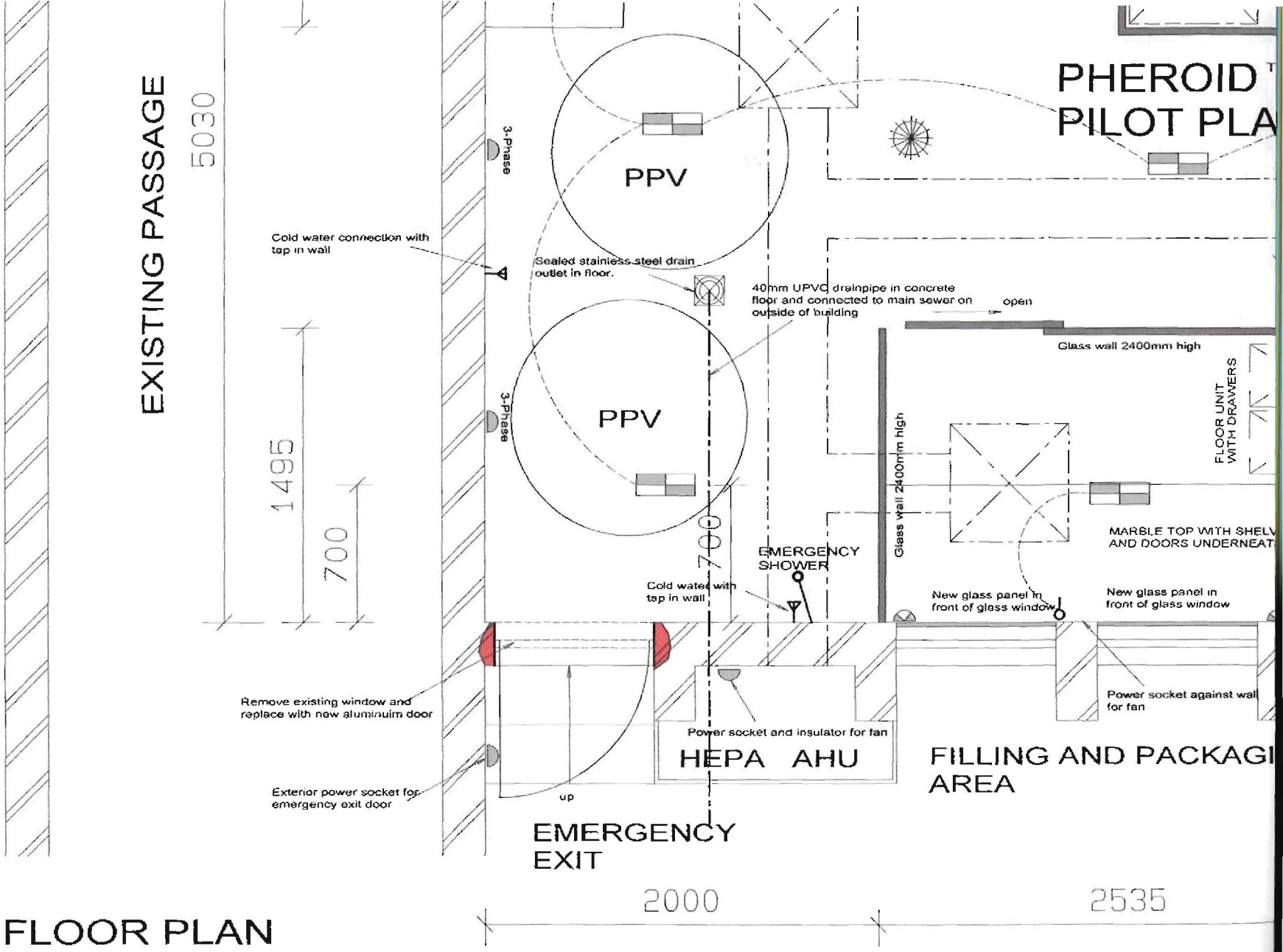
Annexure B

ARCHITECTURAL LAYOUT OF THE PHEROID PILOT PLANT

B.1 Introduction to A2 architectural plan

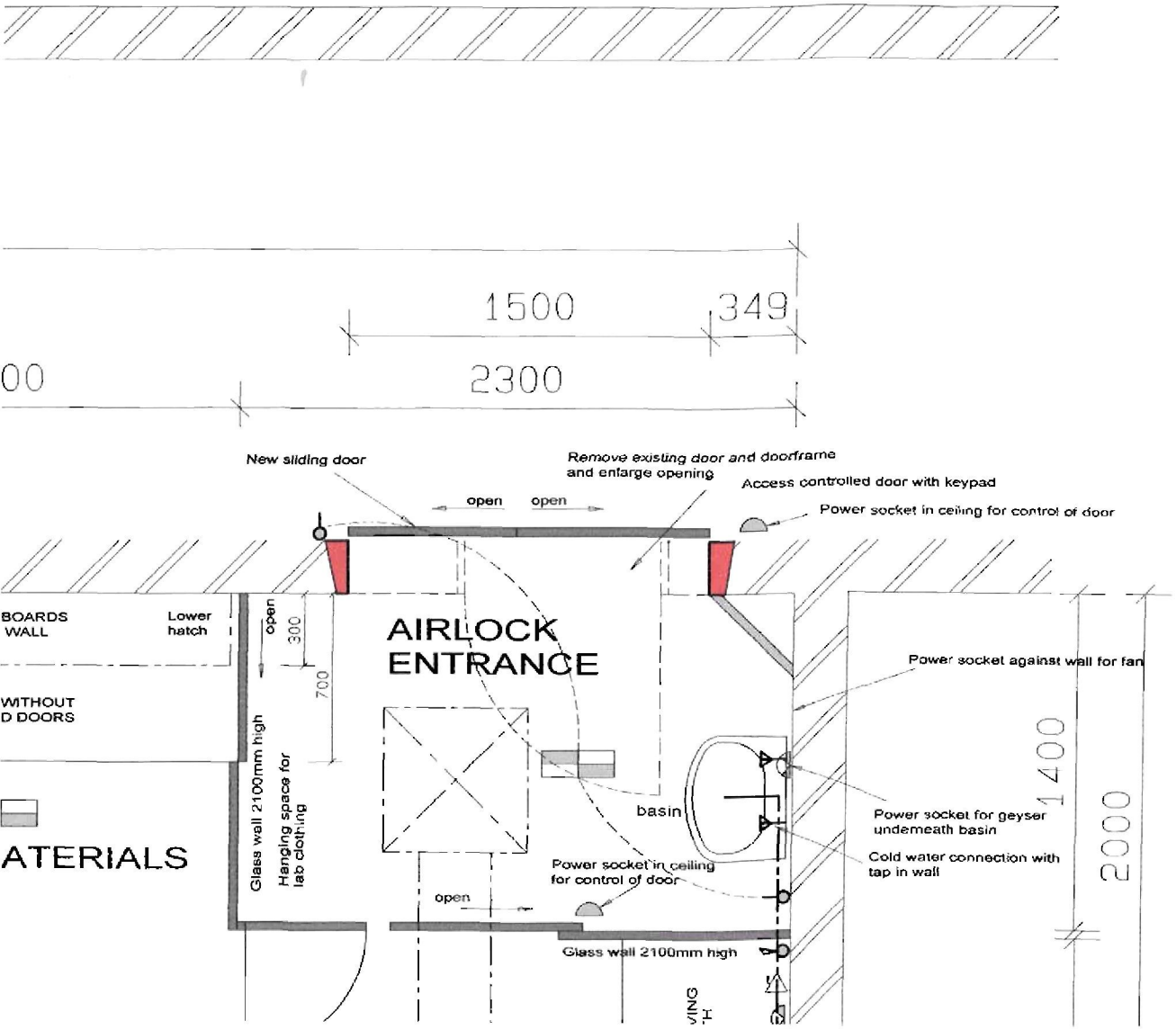
The attached architectural drawing is an A2 sized scaled to 1:20 layout of the architectural plan which has been inserted for the purpose of referencing the design with a greater degree of legibility of the text in the drawing.


7530
1420
1090
665
700
800
1200
Power socket against wall for fan
MICROWAVE OVEN
Glass wall 2100mm high
MARBLE TOP WITH SHELVING AND DOORS
open
Top hatch
500
MARB
SHEL
MARBLE TOP WITH SHELVING AND DOORS UNDERNEATH
WEIGHING AREA
DISPENSING TABLE
Glass wall 2100mm high
RAW
STO
fridge



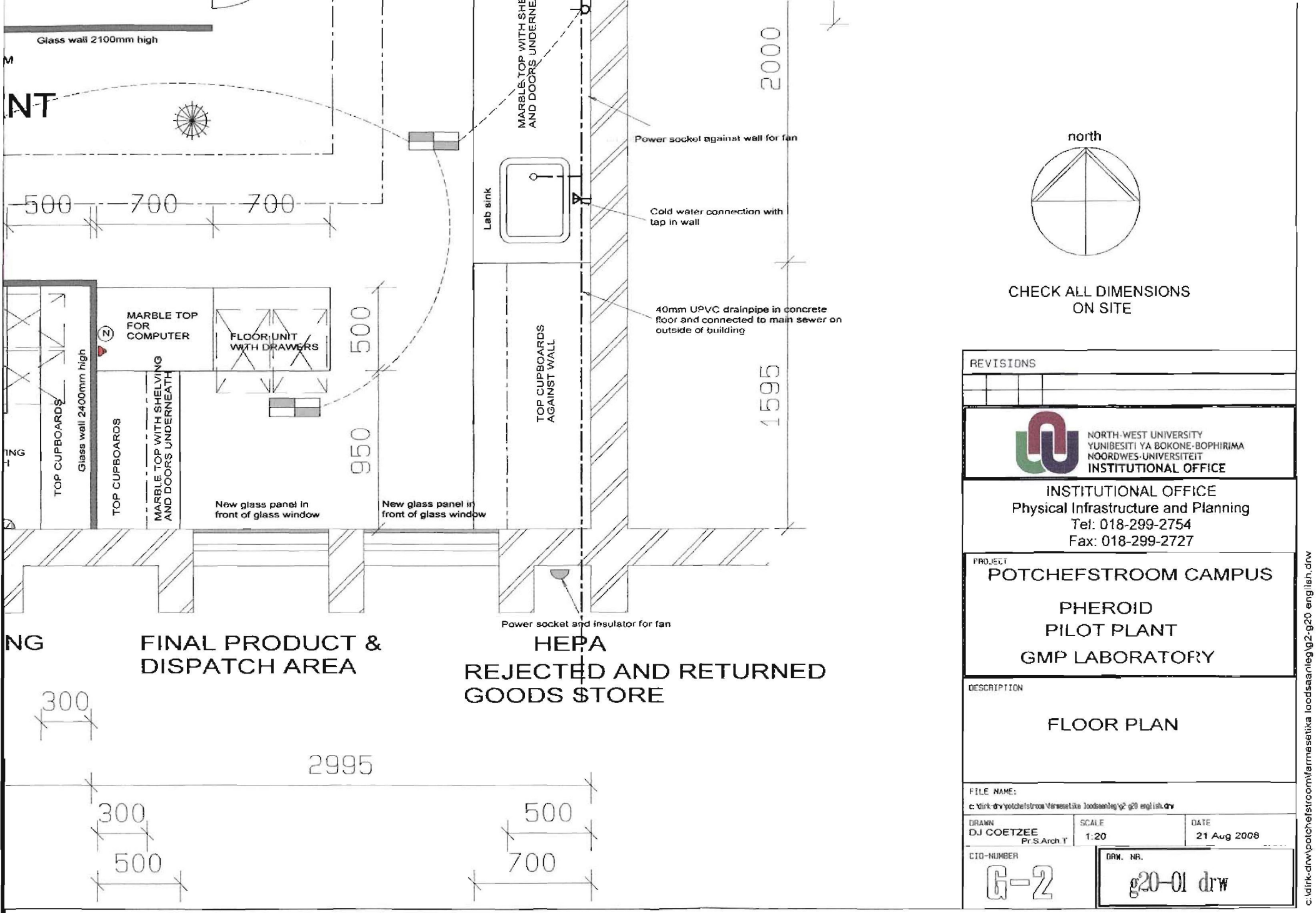
FLOOR PLAN

SCALE 1:20



ELECTRICAL SYMBOLS

	Double power socket 1000mm above ground level
N	Network access point
	Dedicated power socket
	Telephone connection
3-Fase	3-Phase power socket (40A)
	Panic button
	Smoke alarm
	Double fluorescent lights (1200mm)
	Light switch



north

CHECK ALL DIMENSIONS ON SITE

REVISIONS

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YUNIBESITI YA BOKONE-BOPHIRIMA
NOORDWES-UNIVERSITEIT
INSTITUTIONAL OFFICE

INSTITUTIONAL OFFICE
Physical Infrastructure and Planning
Tel: 018-299-2754
Fax: 018-299-2727

PROJECT

POTCHEFSTROOM CAMPUS

PHEROID PILOT PLANT GMP LABORATORY

DESCRIPTION

FLOOR PLAN

FILE NAME:
c:\dirk-drw\potchefstroom\farmasetika loodsaanleg\g2-g20 english.drw

DRAWN	SCALE	DATE
DJ COETZEE Pr.S.Arch.T	1:20	21 Aug 2008

CID-NUMBER	DRW. NR.
G-2	g20-01 drw

c:\dirk-drw\potchefstroom\farmasetika loodsaanleg\g2-g20 english.drw

C.1 Introduction

The purpose of a scientific journal is a means of reporting the findings of the researcher. Various journals are available in all fields of research. The South African Pharmaceutical Journal (SAPJ) has been selected for this study as the journal publishes research in the field of pharmaceutics that are pertinent to pharmaceutical developments within South Africa. The scope of this study is integral to good manufacturing practice; it engages the design of a pilot facility for a novel drug delivery system at an academic institution. This is a novel concept to the South African pharmaceutical industry and for South African pharmaceutical institutions. It is hence deemed to be of interest to the readers of this journal.

The empirical investigations and procedures followed and their findings discussed in the article presented are outlined in Annexure A. This chapter includes information on the author guidelines for the SAPJ, the title page requirements, abstract and the article.

The format and font for the title page and the abstract and article are as per the author guidelines.

C.2 Author Guidelines

When writing a scientific research article, the researcher should adhere to a set of rules regarding the formatting of the article. These rules are known as the author guidelines. These are prescribed by the respective journal. The author guidelines for the South African Pharmaceutical Journal are provided in Annexure B. The format of the article in this chapter, was done according to the prescribed guideline.

C.2.1 Content of Author Guidelines

Electronic, online submissions at www.sapj.co.za/authors are preferred. All new users to the website must register first. Once registered, simply log in, click on "Information for authors" and then on "START SUBMISSION PROCESS". An easy 5 step process guides you through the uploading of your manuscript. All manuscripts must be submitted in MS Word® (not RTF) format using Times New Roman font size 10 and single-spacing. The author must always retain a copy. All the named authors must have approved the final manuscript.

Pages should be numbered consecutively in the lower right corner.

The following contributions are accepted:

Original research

(3200-4600 words) (4-6 pages). Structured abstract (Background, Methods, Results and Conclusion(s).

Pharmacy-orientated clinical reviews

First part:

1-2 pages clinical review of the condition and rationale for selecting drugs and...

Second part:

2-3 pages on the role of the pharmacist (referral criteria/warning signs, dispensing notes (compliance issues, drug interactions etc,) monitoring a treatment response, side-effect management, SAE reporting, generic substitution with particular drug classes). (3200-4600 words)(4-6 pages)

Scientific review articles

Reviews in the following disciplines – pharmaceutics, pharmacology, pharmaceutical chemistry, pharmacy practice, social and administrative pharmacy. (1800-2400 words)

Short clinical updates

(1800 words) (3 pages) Short clinical review to update pharmacist on new developments of a condition – clinically or in the therapeutic approach.

Evidence-Based-Pharmacy-Initiated Pharmacotherapy (EBPIP)

(1800-2400 words)(3-4 pages) Over the counter medication as well as prescription only medication. Important to include clear guidelines on clinical presentations and rationale for drug selection. For OTC medication, must include a section on "when to see your doctor.◆?

Pharmacovigilance

(SAE reporting, clinical articles on identifying adverse drug reactions, reviews on side-effect management (choosing a drug with best side-effect profile (For example Antidepressants and erectile dysfunction – what the pharmacist should know. Myalgia and statins – what pharmacists should know and tell their patients).

Pharmaco-economics

Reviews on the cost-effectiveness of therapy. (2 400 words)(3-4 pages)

Regulations/Policy

(1800-2400 words).

Case studies

A pharmacy case study, (1 200 words) (2 pages).

Critical appraisals of clinical trials

(300 word trial summary and 300 word commentary)(<600 words in total including references).

Scientific Letters

(2400 words) (3-4 pages).

Letters to the Editor

(400-800 words) (1 page).

Open Forum/Opinion paper

(2400 words) (4 pages maximum).

Format

All manuscripts must be submitted in UK English, typed in MS Word, Times New Roman, font size 10. All articles must be proof read by a language specialist or a colleague proficient in English before submission.

Title page

All articles must have a title page with the following information and in this particular order: Title of the article; surname, initials, qualifications and affiliation of each author; name, postal address, e-mail address and telephonic contact details of the corresponding author and at least 5 keywords.

Abstract

All articles should include an abstract. The structured abstract for an Original Research article should be between 600-800 words and should consist of four paragraphs labeled Background, Methods, Results, and Conclusions. It should briefly describe the problem

or issue being addressed in the study, how the study was performed, the major results, and what the authors conclude from these results. The abstracts for other types of articles should be no longer than 250 words and need not follow the structured abstract format.

Keywords

All articles should include keywords. Up to five words or short phrases should be used. Use terms from the Medical Subject Headings (MeSH) of Index Medicus when available and appropriate. Key words are used to index the article and may be published with the abstract.

Web-long, paper-short policy for original articles

The full text of original research articles will be available online only. The structured abstract (up to 800 words) will be published in hardcopy and the reader will be referred to the open access website to print the full copy if required.

Acknowledgments

In a separate section, acknowledge any financial support received or possible conflict of interest. This section may also be used to acknowledge substantial contributions to the research or preparation of the manuscript made by persons other than the authors.

References

Cite references in numerical order in the text, in superscript format (Format> Font> Click superscript). Please do not use brackets or do not use the foot note function of MS Word. In the *References* section, references must be typed double-spaced and numbered consecutively in the order in which they are cited, not alphabetically. The style for references should follow the format set forth in the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*(http://www.icmje.org) prepared by the *International Committee of Medical Journal Editors.*

Abbreviations for journal titles should follow *Index Medicus* format. Authors are responsible for the accuracy of all references. Personal communications and unpublished data should not be referenced. If essential, such material should be incorporated in the appropriate place in the text. List all authors when there are six or fewer; when there are seven or more, list the first three, then "et al". When citing URLs to web documents, place in the reference list, and use the following format: Authors of document (if available). Title of document (if available). URL. (Accessed [date]).

The following are sample references:

1. London L, Baillie R. Notification of Pesticide Poisoning: Knowledge, Attitudes and Practices of Doctors in the Rural Western Cape. S A Fam Pract 1999;20(1):117-20.
2. FDA Talk Paper: http://www.fda.gov/bbs/topics/ANSWERS/2002/ANS01151.html (Accessed 04/10/2002).

   More sample references can be found at: http://www.nlm.nih.gov/bsd/uniform_requirements.html

Tables

Tables should be self-explanatory, clearly organised, and supplemental to the text of the manuscript. Each table should include a clear descriptive title on top and numbered in Roman numerals (I, II, etc) in order of its appearance as called out in text. Tables must be inserted in the correct position in the text (not at the end).

Authors should place explanatory matter in footnotes, not in the heading. Explain in footnotes all non-standard abbreviations. For footnotes use the following symbols, in sequence:

*,†,‡,§,||,**,††,‡‡

Figures

All figures must be inserted in the appropriate position of the electronic document. Symbols, lettering, and numbering (in Arabic numerals e.g. 1, 2, etc. in order of appearance in the text) should be placed below the figure, clear and large enough to remain legible after the figure has been reduced. Figures must have clear descriptive titles.

Photographs and images

If photographs of patients are used, either the subject should not be identifiable or use of the picture should be authorised by an enclosed written permission from the subject. The position of photographs and images should be clearly indicated in the text. Electronic images should be saved as either jpeg or gif files. All photographs should be scanned at a high resolution (300dpi, print

optimised). Please number the images appropriately.

Permission

Permission should be obtained from the author and publisher for the use of quotes, illustrations, tables, and other materials taken from previously published works, which are not in the public domain. The author is responsible for the payment of any copyright fee(s) if these have not been waived. The letters of permission should accompany the manuscript. The original source(s) should be mentioned in the figure legend or as a footnote to a table.

Review and action

Manuscripts are initially examined by the editorial staff and are usually sent to independent reviewers who are not informed of the identity of the author(s). When publication in its original form is not recommended, the reviewers' comments (without the identity of the reviewer being disclosed) may be passed to the first author and may include suggested revisions. Manuscripts not approved for publication will not be returned.

Ethical considerations

Papers based on original research must adhere to the Declaration of Helsinki on "Ethical Principles for Medical Research Involving Human Subjects" and must specify from which recognized ethics committee approval for the research was obtained.

Conflict of interest

Authors must declare all financial contributions to their work or other forms of conflict of interest, which may prevent them from executing and publishing unbiased research. [Conflict of interest exists when an author (or the author's institution), has financial or personal relationships with other persons or organisations that inappropriately influence (bias) his or her opinions or actions.]*

*Modified from: Davidoff F, et al. Sponsorship, Authorship, and Accountability. (Editorial) JAMA 2001: 286(10)

The following declaration may be used if appropriate: "I declare that I have no financial or personal relationship(s) which may have inappropriately influenced me in writing this paper."

Submissions and correspondence

All submissions and correspondence regarding manuscripts should be addressed to Lorraine Osman, E-mail: lorraine@pharmail.co.za or an electronic copy on CD may be sent to, The Editor, SAPJ, PO Box 26039, Arcadia, 0007

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. The submission has not been previously published, nor is it before another journal for consideration (or an explanation has been provided in Comments to the Editor).
2. The submission file is in Microsoft Word document file format.
3. All URL addresses in the text (e.g., http://pkp.sfu.ca) are activated and ready to click.
4. The text is single-spaced; uses a 10-point font; employs italics, rather than underlining (except with URL addresses); **and all tables and figures are placed within the text at the appropriate points**, rather than at the end.
5. The text adheres to the stylistic and bibliographic requirements outlined in the Author Guidelines, which is found in About the Journal.
6. Electronic images are saved as either jpeg or gif files. All photographs were scanned at a high resolution (300dpi, print optimised) and saved/numbered appropriately corresponding with the text.
7. All tracking changes in the document must have been accepted before sending it to SAPJ.
8. Have you asked a colleague or language expert to proofread your final manuscript?
9. All supplementary files such as survey instruments or scanned photographs are separated from the main text and will be uploaded as supplementary files.
10. In the case of a research paper, prior approval has been obtained from a research ethics committee, and this fact is declared in the methods section of the manuscript.

SA Pharmaceutical Journal | ISSN 1015-1362

C.3 Article for the South African Pharmaceutical Journal

C.3.1 Title Page

The title page includes the following as per the author guidelines:

THE DESIGN OF A PILOT PLANT FOR THE PRODUCTION OF PHEROID BASED PRODUCTS IN AN ACADEMIC ENVIRONMENT

Padayachee, S. (B.Pharm), Grobler, A.F. (M.Sc.), Kotzè, A.F. (Ph.D.) and Liebenberg, W. (Ph.D.).

Corresponding Author: Padayachee, S.
Postal Address: Private Bag X6001, Internal Box 36, Potchefstroom, 2520
Email address: silverani.padayachee@nwu.ac.za
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Keywords: Pheroid™ Technology, Pilot facility design, GMP, Academic Institutions

Comments to the Editor: This article forms part of a MSc dissertation of which the co-authors are the supervisor and co-supervisor of the study. The article has not been previously published.

C.3.2 Abstract

The abstract as outlined by the SAPJ author guidelines is presented below:

ABSTRACT

THE DESIGN OF A PILOT FACILITY FOR THE PRODUCTION OF PHEROID™ BASED PRODUCTS IN AN ACADEMIC ENVIRONMENT

Background

The emerging trend of establishing cGMP production facilities at academic institutions is providing a welcome opportunity for university researchers involved with pharmaceutical R & D. While the primary business of universities is education, university researchers are excited about the service opportunities that this innovation can provide for expediting early phases of clinical trials. Research at the North-West University (NWU) in South Africa on Pheroid™ technology (a novel drug delivery system) has reached stages of early clinical trials. Challenges of acquiring the investigational drug from consulting manufacturing organisations (CMO) are numerous and such delays could invariably stall the availability of novel safe and effective drug therapies. NWU has considered the innovation of establishing a pilot production facility on the campus for the production of investigational drug product. The scope of this study was to investigate the requirements and to propose a design of a pilot facility for the production of Pheroid based products on the NWU campus.

An evaluation of a low budget purely theoretical design based on process and GMP requirements was evaluated for feasibility using practical engineering.

Commercial and academic production facilities are governed by the same national regulations, but have different resources, business practices and goals. Good Manufacturing Practice (GMP) is a system for ensuring that products are consistently produced and controlled according to quality standards. Pharmaceutical production facilities in South Africa are regulated and guided by the South African Medicines Control Council (MCC).

Methods

The approach of the investigations were qualitative. A chronological sequence of enquiries and investigations were conducted. These were as follows; (1) Interviews with NWU R&D project co-ordinators for feasibility and site allocation, (2) Observations, document collection and photographs of the allocated site, (3) Interviews, observations of Pheroid production process, document viewing of the

experimental production process, (4) Presentation and practical evaluation of proposed theoretical model (model 1), (5) Presentation and evaluation of model 2, (6) Presentation and evaluation of model 3, (7). Presentation and evaluation of model 4.

Results

The facility design process involved the integration of corporate philosophy, user requirements, process knowledge, critical parameters, regulatory requirements, financial support and good engineering practice. The findings cannot be generalised to all facilities as the Pheroid production process is unique. Certain factors have influenced the design of the facility. These factors include material flow, product and personnel flow, level of product, personnel and environmental protection, space and budget limitations. The finding yielded that design models based on the regulatory requirements and process requirements are influenced by space and cost limitations. The findings reveal that several non-GMP requirements such as worker safety and environmental conditions are contributors to the design of the facility. Process requirements, such as heating of process material in a confined space, may impact negatively on safety and worker comfort. In such a circumstances (small facility size) alternate methods of achieving process requirements without compromising product quality and worker safety were to be considered.

Pheroid once formed has the ability to entrap particles and may entrap particulates in the environment. Hence the level of protection of the manufacturing environment from particulate contamination has to be controlled. The use of containment mechanisms in facility design are necessary to minimise the risk of contamination. Containment of active drug substances such as anti-tuberculosis agents and anti retrovirals from the outer campus environment was also considered in the facility design. The use of isolator barrier technology rendered more cost effective on installation but was practically not feasible with high maintenance demands. The use of a HVAC system to achieve the desired level of protection was practically feasible and much more expensive. Protection through containment of the Pheroid production process was necessary considering the nature of the Pheroid. The design of the facility necessitated consultation on air handling systems and good engineering practice.

Conclusion

A conceptual design has been established for a pilot facility at NWU campus. The size of the allocated site presented the largest challenge and has resulted in containing most of the Pheroid production processes to the Pheroid pressure vessel. The Pheroid production facility would therefore be considered incomplete without the Pheroid pressure vessel.

As there are no prescribed approaches to pharmaceutical facility design. The process should be guided by regulations on what should be done to achieve GMP compliance. The observable movement in the field of pharmaceutics towards greater technical complexity makes facility design increasingly specialised to the field of pharmaceutical engineering rather than only to the application of pharmaceutics. This perhaps is an indicator that the training of pharmaceutics should be inclusive of pharmaceutical engineering. That facility design requires cooperation of all units such as the quality assurance, engineering contractors as well as the commissioning contractors.

The project offered further realisation that the designer of any pharmaceutical facility should have a sound understanding of the national regulatory requirements, an understanding of the institutions/ manufacturers requirements, understand the purpose of the facility, understand the corporate philosophy, provided with information on the manufacturing process such that an appropriate design philosophy can be established. The available financial support should not be underestimated. The design process should be driven to generate the most suitable model rather than allowing for cost to be a design limiting factor.

C.3.3 The Article

THE DESIGN OF A PILOT PLANT FOR PRODUCTION OF PHEROID BASED PRODUCTS IN AN ACADEMIC ENVIRONMENT

Pilot facility at University campus

On reaching the early phases of clinical trials university researchers outsource the production of trial products. This can be a daunting challenge as newer technologies often involve the use of specialised equipment and specialised processing needs that contract manufacturers are not willing to procure for pilot scale contracts. As the primary business of academic institutions is education, many institutions overlook the benefits of innovations such as a production facility on campus. For instance, researchers at North-West University (NWU), dedicated to production of a novel drug delivery system namely the Pheroid technology has the potential benefits of cost effectiveness, efficiency, time saving, resources such as existing premises, expertise and equipment. More significantly it provides learning exposure of students to the production environment. As a training facility the confidentiality of university research projects are better protected. The (NWU) has considered this option, hence the scope of this study has focused on designing a GMP compliant pilot pharmaceutical facility at NWU campus. The facility would be a dedicated pilot production facility for Pheroid based formulations.

From research lab to pilot facility

In general the attitude of academic institutions towards facilities on campus are misconceived as being another type of laboratory.[1] Formulation developments on campus generally take place in research or experimental labs, the question is, why create another laboratory when the product can be produced in the research laboratory? The difference between a research laboratory and pilot facility has contradictions between activities, that is, the pilot facility requires full GMP (Good Manufacturing Practice) compliance while the other is focussed only on experimentation and development.[2] Batches produced for clinical trials and pilot batch studies for stability determination have to be manufactured according to GMP standards and are to be carefully documented.[3] A research laboratory of dimensions 7,55 x 5, 04 m was allocated for the purpose of establishing a pilot facility. Establishment of a facility can only be meaningful if adequate planning and appropriate design philosophies are engaged. The designer should understand that the objective would be to deliver a design for a licensed facility and not just a design of a building filled with equipment.[4] This study involved using regulatory guidelines, requirements of Pheroid production, user requirements and literature on facility design to establish a theoretical model of the facility.

Methodology

The approach of the investigations were qualitative. A chronological sequence of enquiries and investigations were conducted. These were as follows; (1) Interviews with NWU R&D project co-ordinators for feasibility and site allocation, (2) Observations, document collection and photographs of the allocated site, (3) Interviews, observations of Pheroid production process, document viewing of the experimental production process, (4) Presentation and practical evaluation of a proposed theoretical model (model 1), (5) Presentation and evaluation of model 2, (6) Presentation and evaluation of model 3, (7). Presentation and evaluation of model 4.

Pilot Facility Design

The purpose of a pilot facility would be to produce a pilot scale batch in a way that meaningfully simulates the potential full batch size, such that the quality of the product would be assured. That this quality would be consistent on repeated production of the same product. Pilot facilities are not only critical in the establishment of the drug manufacturing process and in performing process validation but also for setting the standards for good manufacturing practice.[5] A regulatory requirement for pharmaceutical product manufacture is that the product be manufactured in accordance with GMP.[3] Hence, the role of commercial pilot facilities become increasingly diminished as pilot scale batches can be manufactured in a full scale commercial pharmaceutical facility. Pilot facilities on campus therefore has to be designed and approved to be GMP compliant. The South African GMP guidelines state that, "Products intended for use in clinical trials (late Phase II and Phase III studies) should as far as possible be manufactured at a licensed facility, e.g. a pilot plant primarily designed and used for process development."[3] The need to ensure GMP compliance in academic institutions may involve including provisions in the design and in procedures that would allow for the sharing of spaces and optimise the use of trained and qualified personnel.

GMP

What is GMP and how does it affect facility design?

Good Manufacturing Practice (GMP) is a system for ensuring that products are consistently produced and controlled according to quality standards. It is designed to minimise the risks involved in pharmaceutical production that cannot be eliminated through testing the final product and therefore the need for compliance.[6] GMP covers all aspects of production; from the starting materials, premises and equipment, to the training and personal hygiene of staff. GMP must include the provision of systems to provide documented proof that correct procedures are consistently followed at each step in the manufacturing process each time the product is made.[7] As the pilot facility to be designed is based in South Africa, it would be imperative to identify the facility GMP requisites as per the national regulatory guidelines.

While it can be assumed that regulations require a disciplined approach to the design of pharmaceutical manufacturing facilities, these are not prescribed.[4] Experience from various contributors to the ISPE guides has elaborated that the approach would be rather that of ensuring good design practices that forms the foundation for the design of a suitable manufacturing facility. The foundation of good design practice (GDP) involves taking into consideration the manufacturing process(es) and the product (s) that would be produced, tested, or held in the facility under design.[4] Majority of design decisions and design criteria should be based on the critical quality attributes of the product, hence the designer must have knowledge of how the facility should operate and how it would be validated.[4] During the development of the design, the manufacturing process and facility requirements are defined. These are to be developed through discussions with the end user, including the manufacturing, Quality Assurance (QA) / Quality Control (QC) staff, engineering , validation and constructor groups.[4]

PHEROID™

Pheroid technology is a patented drug delivery system that presents key advantages of enhanced delivery of known active drug substances, reduced time to onset of action, reduction of minimal effective concentration, increased therapeutic efficacy, reduction in cytotoxicity, penetration of most known barriers in the body and in cells, ability to target treatment areas, lack of immunological response, has the ability to transfer genes to cell nuclei and show reduction of drug resistance.[8] Whilst there are many existing delivery system technologies such as lipid-based carriers or viral vectors, the Pheroid is unique among these in that its components are manipulated in a very specific manner to ensure its high entrapment capabilities, very fast rate of transport, delivery and stability. The absorption capabilities and drug release characteristics of the Pheroid can thus be controlled. The entrapment of actives within the Pheroid creates a safer, more effective formulation than one involving the said active alone.[9]

In contrast with liposome's, Pheroids are formulated by a self assembly process similar to that of low-energy emulsions and micro-emulsions and no lyophilisation or hydrations of the lipid components are necessary. Pheroids are dispersed within a dispersion medium as in emulsions and contains not only two liquid phases but also a dispersed gas phase which is associated with the fatty acid dispersed phase.[10] The Pheroid system hence is substantially different from conventional macromolecular carriers such as liposomal delivery systems. Pheroid does indeed meet the criteria to be classified as a nanoparticle. It however does not fit with the four particle engineering technologies.[11] The formation of Pheroid is largely based on gassing with nitrous oxide N_2O. The stable Pheroid vesicular structures are indicated in molecular modelling to be formed due to the interaction between the fatty acids and nitrous oxide. The nitrous oxide essential fatty acid (NOEFA) matrix is the basis through which the Pheroid can be effectively used as a novel drug delivery system to transport both hydrophobic and hydrophilic drug substances.[10]

The Pheroid can also be said to comply with characteristics of microsphere formation, but however fail to move beyond the solution phase into either gel or glass state.[12] Though the Pheroid shows similarities to some features of the nanoparticle, its formation does not conform to the documented mechanisms of nanotechnology formations.

Facility design considerations

The following factors that contribute to the quality or lack thereof in the final product are starting materials; packaging materials; validated processes; personnel; procedures; equipment; design and quality of premises and manufacturing environment.[3]

The ISPE baseline guidelines, the South African GMP guideline and the WHO guidelines were extensively consulted for purposes of being able to draft a theoretical design of the pilot facility. Some aspects discussed with the findings are; process, equipment, requirements, GMP requirements, architectural requirements, worker safety and worker comfort requirements.

Findings and rationale for a theoretical model

As novice designer, a theoretical model was to be proposed as a conceptual model prior to the development of an architectural design. The theoretical model would take into consideration the Pheroid process, user, GMP and regulatory requirements. A model constructed on the applications of concepts from literature provided the basis of the theoretical draft.

The establishment of the process requirements and process flow are achieved through understanding the manufacturing process such that the necessary support systems to facilitate the process should be given consideration as these could impact on the quality of the product and the efficiency of operations.[4] The Pheroid production process involves gassing with N_2O for a period of four days under pressure, heating of ingredients to 75°C and then cooling. The dosage forms produced at the pilot facility would be oral liquid and topical dosage form. This raised a concern that impacted on worker safety and comfort as the scaled up batch production would generate too much heat on open surface and the transfer of heated materials in a confined space increases the risks on worker safety. The feasibility of the plant was hence negative based on the process and worker comfort and safety.

The consideration of containing most of the production process into a vessel was recommended as an alternative such that the risk of worker injury be reduced, the gassing does take place in a pressurised vessel which could be designed to contain the heating, cooling and mixing processes. The containing of the process also presents an advantage in that the risks of contamination are reduced. The pheroid has a property of entrapping particles and hence the containment would reduce the risk of entrapping unwanted particles. From this it is noted how factors such as the premises, equipment and containment have been beneficial in enabling more safer and efficient processing of the Pheroid in a smaller space. The principles set out for premises and equipment are such that they would be located, designed, constructed, adapted and maintained to suit the operations to be carried out. These should be designed or the layout should be such that it minimises the risk of errors, the risk of contamination and or cross-contamination and facilitate adequate cleaning.[3] This conforms with the fact that there is an increased use of containment to reduce staff exposure to potentially harmful materials and conditions.[2] The two factors that significantly affect the manufacturing environments are:

Materials management

The receipt, handling, storage and dispensing of raw materials, in process, bulk final and finished final product should be concurrent with the cGMP principles. Dedicated areas, prevention of contamination and cross-contamination, use of approved raw materials in production and sampling are components of good manufacturing practices which can dictate to a large extent the design of the facility and locations and characteristics of various dedicated areas.[3]

Equipment

The nature and type of equipment used in a facility contributes essentially to the layout of the facility. Production process, dedicated areas, clean in place (CIP) systems as well as equipment contributes to deciding on the facility design process to accommodate the cleaning process as well as the processing and technology involved in the production. The introduction of the Pheroid vessel as equipment is a necessity for the pilot facility. The design would have to accommodate for the housing, operations and movement of this equipment.

Thoughtful consideration of facility design and related GMP matters will encourage greater safety of materials produced for study subjects, patients as well as staff protection.[6]

The draft theoretical design has also taken into account the non GMP component of containing the movement of particulates out of the manufacturing environment. This is to reduce the risk of organism resistance to the actives used (this was a user request). The level of protection required for Pheroid production had to also be taken into consideration.

An increase in automation and safety considerations with regards to the substances used in order to reduce staff and product exposure has resulted in an increased use of air extractors/airflow units in production facilities. There are set standards and regulations that set out requirements for safe working practices and these have a major influence on the layout and design of the facility.[13] Process factors may also require specific manufacturing environments for the manufacture of products.

A cleanroom has a *controlled* level of contamination that is specified by the number of particles per cubic meter at a specified particle size. The risk of product contamination is to be evaluated and suitable preventative methods should be identified which may reduce this risk to an acceptably low level.

Often not all areas of an oral dosage facility require the same level of protection. Each area should be evaluated based upon its function, which may vary at different times and with different products. The degree of contamination risk is based primarily upon the duration of exposure to the environment and the number of product changeovers and mix within the facility. In general the greater these factors the greater

the need for product protection by architecture or engineering systems. [14] For Oral Dosage facilities three levels of protection are to be considered.
"Level 1 - General. An area with normal housekeeping or maintenance. Level 2 - Protected. An area in which steps are taken to protect the exposed product and materials, which will become part of the product from degradation. These steps may be procedural. Level 3 - Controlled area, is an area in which specific environmental conditions are defined, controlled and monitored to prevent degradation of the product (or materials which will become part of the product)."[14]

Product protection factors:
Determining an appropriate level of protection for each area of the facility requires consideration of the following:
Product Characteristics: Each product characteristic should be reviewed and evaluated for impact upon facility requirements. Product characteristics include toxicity or potency, physical properties such as density and physical state, hygroscopicity, cleanability, light sensitivity and others.
Process Considerations: These include;

i. Materials receipt, storage and protection methods.
ii. Specific unit operations such as weighing, dispensing, blending/mixing, finished dosage and their arrangement.
iii. Material transport and handling.
iv. Methods for packaging and storage.

Facility Flexibility: This refers to the number of different products processed within the facility or a particular area of the facility. The facility may process:

i. A single product. It implies no flexibility. Foreign contamination would be the primary concern.
ii. Multiple Products in dedicated equipment. It implies moderate flexibility. Contamination between areas of the facility would be an additional major concern.
iii. Multiple products in multi-use equipment. It implies high flexibility. Contamination within a process (equipment) and/or the individual processing area is possible. In these areas the number and frequency of product changeovers and the type of cleaning procedures directly affects the degree of contamination risk.

Based on this an isolator area was set up that was to achieve level 3 protection and was the area in which the actives were to be added after the Pheroid base was formed. The weighing area for pheroid ingredients were enclosed and a level 2 protection was allocated. The filling and packing area was enclosed and had to achieve level 2 protection. The rest of the areas were operative at level 1. The isolator area had to have a negative pressure relative to the central region and the weighing area had to also be positive to the central region, this was such that particles would move from positive to less positive regions hence reducing the chances of contamination. The isolator unit would have two HEPA filters for incoming and outgoing air for purposes of reducing the movement of active ingredient particles to the outer environment.

The model includes a raw material store separating the quarantined goods from the approved goods; weighing area that is enclosed, the Pheroid vessel and mixing area, a bulk in process area, a filling and packing area, a storage area for printed packing and a store for unprinted packing, a goods despatch area, a goods reject and returned area, these areas are to be governed by the relevant documentation. Documentation is an essential component of GMP and includes: specifications, manufacturing formulations and instructions, procedures and records. Documentation should be free from errors and be available in writing such that errors in communication are avoided. In this way traceability of processes could be assured. Academic institutions may have to evaluate their procedures more frequently than their industrial counterparts. For a facility design of multiple product operations this may prove critical in keeping with the continuum of cGMP if the design is limited due to space or limited resources (such as availability of several mixing vessels or skilled technicians). Whilst standard operating (SOPs) are established to ensure process reproducibility, these may also be beneficial in creating ways of ensuring that good practices are adhered to especially if these cannot be incorporated into the existing facility design.[3]

Practical evaluation of the Theoretical model
This theoretical model was evaluated by a consulting engineer. The achievement of the pressure differentials over a space of a metre (central space) was not feasible as the pressure differences would create turbulence and interfere with the weighing. The cost of fitting an isolator unit would be the same as

making the entire facility a cleanroom. From the practical perspective the theoretical design failed to meet the GMP criteria. A re-work of the theoretical design included an airlock such that particulate movement into and out of the facility was controlled. A Heating Ventilation and Air conditioning (HVAC) system was to be used to achieve the level of protection desired for the facility.

As the practicality of an isolator system was not feasible, the use of the HVAC system was considered to achieve the required level of protection. The entire room was to be made a level 2 protection area and fitted with HEPA filters for air into and a HEPA filter for air out of the facility. The diffusers was to be located on the right wall of the facility and the extractor on the opposite left wall relative to the entrance. The dedicated raw material area was resized due to the absence of the isolator unit and the utilities were moved to more practical locations to ease the flow of materials and personnel. This was possible due to the availability of added funding. The theoretical model had been based on a low budget. Thus an important consideration is the necessity for adequate financial support in facility design.
The evaluation of the redesigned theoretical model revealed that the desired level 2 protection was only possible if it achieved an air change rate of 1cubic metre per second which differed from the average 20 air changes[14]. The rate of air changes required can be calculated for the desired level of protection.
Air Supply= Room Volume x No of Air changes/3600s therefore the Air supply =(2.4x5x7.5) x 40 /3600s = 1.08 cubic metres per second.
Thus 40 air changes would be required to achieve a level 2 or ISO 7 protection within the facility. The layout of the diffuser and extractor was said to allow the air to flow horizontally across the room hence not providing the protection required. The recommendation was to use a few terminal diffusers from the ceiling down and the extractors located lower down such that the airflow does in fact reach the respective areas within the facility without creating much turbulence to achieve the desired level of protection.
The model was reworked and ultimately the integration of the practical/technical aspects of facility design with that of the theoretical components was drafted. This led to the first concept design of the facility. Various components to the GMP approach to facility design were considered it is extensive and has for practical reasons been omitted from this article.

Conclusions
A conceptual design has been established for a pilot facility at NWU campus. The size of the allocated site presented the largest challenge and has resulted in containing most of the Pheroid production process to the Pheroid pressure vessel. The Pheroid production facility in essence is incomplete without the Pheroid pressure vessel.

As there are no prescribed approaches to pharmaceutical facility design the process should be guided by regulations to achieve GMP compliance. However, the observable movement in the field of pharmaceutics towards greater technical complexity makes facility design increasingly specialised to the field of pharmaceutical engineering rather than only to the application of pharmaceutics. This is an indicator that the training of pharmaceutics should be inclusive of pharmaceutical engineering. That facility design requires cooperation of all units such as the quality assurance, engineering contractors as well as the commissioning contractors and that this should commence during the deign planning phase.

The study offered further realisation that the designer of any pharmaceutical facility should have a sound understanding of the national regulatory requirements, an understanding of the institutions/ manufacturers requirements, understand the purpose of the facility, understand the corporate philosophy, is provided with information on the manufacturing process such that an appropriate design philosophy can be established.[4] The available financial support should not be underestimated. The design process should be driven to generate the most suitable model rather than allowing for cost to be a design limiting factor. The design should not be based only on theory and guidelines but is to be a consultative process to achieve the regulatory GMP requirements that are practically feasible.

There are no differences in regulatory requirements for pilot facilities, facilities at academic institutions or commercial facilities. All facilities should be GMP compliant to be able to produce any medicinal product. Investigational products are to meet the same standards of quality as commercially produced products.
The only significant difference with academic institutions, stems from the likely shift from the traditional role of being the point of transfer of technology to industry to continuing with the process to marketing phase.

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