Appendix I Heathside Report

Budget Capital and Operational Costing Study

for

Poppy for Medicine Projects in Afghanistan

Contents:

About Heathside Information Services

1. Introduction
2. Prolonged-release morphine tablets
3. Analysis of data – schedules of equipment and areas for opium extraction and purification
4. Analysis of data – schedules of equipment and areas for production of morphine tablets
5. Equipment Costings
6. Facility Costings
7. Operational Costs
8. Conclusions and Recommendations

Attachment 1 – Secondary Manufacturing Schedule of Areas without Prolonged Release Product

Attachment 2 - Secondary Manufacturing Schedule of Areas with Prolonged Release Product

Attachment 3 – Schedule of Areas for API Manufacture

Attachment 4 – Equipment Costings without Prolonged Release Products

Attachment 5 – Equipment Costings with Prolonged Release Products

Attachment 6a – API Equipment Costings Option 1

Attachment 6b – API Equipment Costings Option 2

Attachment 6c – API Equipment Costings Option 3

Attachment 7 – Quotation from Azopharma

About Heathside Information Services

Based in Devon in the United Kingdom, Heathside Information Services Ltd. provides technical consultancy in the fields of pharmaceutical manufacturing, education and training, and management Information Systems.

1. Introduction

This study investigates the set-up and operational costs for three models of local Afghan processing plants, designed to convert raw opium paste into packaged morphine tablets for sale on the worldwide market. The three models investigated in this report are designed to process respectively 1, 3, & 5 tonnes of raw opium paste.

The stated requirement is for each to produce morphine sulphate 10mg tablets, and, if economically and technologically feasible, to produce prolonged release morphine tablets in 10mg, 30mg, and 60mg strengths. Each factory is to be equipped to extract the morphine from the opium paste, purify it, manufacture tablets from the purified extract, and package the tablets for export.

As the yield of morphine sulphate from opium represents only about 10% of the raw opium weight, the three factories will have initial quantities of active material of only 100kg, 300kg, and 500kg. Assuming equal quantities of each of the three tablet strengths, this is equivalent to approximately 1.2 million of each per 1 tonne of raw opium. These are very small quantities, and, even using the slowest commercial tablet press, the time required to produce the total annual output of morphine tablets will be approximately 12 weeks for the 5 tonne processing plant, with correspondingly lower production times in the other plants. Consequently, if the plants are to be economically viable and self-financing, it will be important for the plants to have other products in their programs. Codeine phosphate tablets, with the codeine being also extracted from the raw opium, will be an obvious additional product, but it will be necessary to include other simply made and locally needed tablets.

The quantities of morphine to be produced are so small as to make the production of Prolonged Release tablets extremely uneconomic, and very unlikely to be of any interest to potential licensors for such tablets. There are a number of prolonged/controlled release formulations on the world market, but, to date, no suppliers have indicated any readiness to open discussions on licensing. It should be noted that the facilities for producing these products will be much more sophisticated than those for simple release tablets, involving complex granulation and coating equipment, and probably requiring the use of flammable solvents, with associated additional capital and operational costs. It should also be noted that the majority of prolonged/controlled release products are presented as capsules, so the cost of equipping to produce these has been included.

In order to make licensing attractive to potential licensors, and to make the production financially viable, it is suggested that the minimum production would need to be in excess of 20 million tablets or capsules. As the usual strength of prolonged release morphine tablets or capsules is 50mg or stronger, this would require at least 10 tonnes of opium paste. Consequently, whilst the plants could later be expanded to provide facilities for the production of these products, it is suggested that this aspect of the project should be left in abeyance pending a substantial increase in the weight of opium to be processed.

The factories will obviously be a prime target for theft, with the refined morphine being very attractive to heroin producers. Consequently, security installations and on-going site security will be major considerations both in set up and operational costings. As the scope of this study is not to include the building shell costs, it is assumed that the security fencing, guardroom, and other security costings will be done locally.

It is understood that the initial markets for the products will be Brazil and certain European Union countries. Consequently, it will be essential to ensure that the facilities are designed and operated to full international standards of GMP.

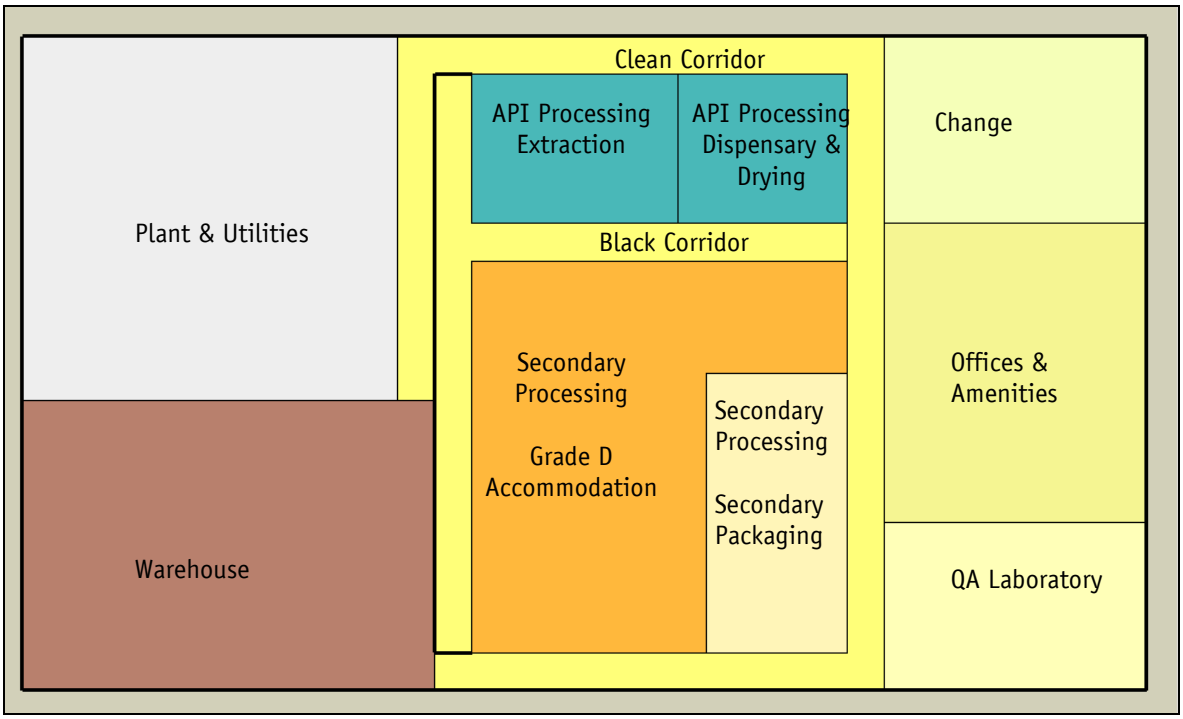
As agreed in the contract terms, Heathside Information Services Ltd are providing the following within the body of this report:

1. An outline method for converting fresh opium into (1) morphine sulphate 10mg tablets and (2) prolonged release (see above) 10mg, 30mg, & 60mg morphine tablets. The extraction and purification methods are to be based on the Indian model, which has been provided by The Senlis Council. It takes full account of all environmental factors and constraints in Afghanistan. The costs and processes involved in drying the fresh opium in ovens are included.
2. Outline set-up costs for three tabletting facilities, the three facilities having the capacity to convert, respectively: 1 tonne, 3 tonnes, and 5 tonnes of opium into morphine sulphate 10mg tablets as well as prolonged release tablets (identified as additional costs). These costs shall include, but not be limited to (1) the costs of machinery and equipment, with reference to country of origin and manufacturer where available (2) the costs of drying fresh opium in ovens (3) the costs of packaging. These costs shall not include any local costs such as building of the factory, transportation, and labour costs.
3. Outline running costs for the three facilities referred to in 1 & 2. These costs shall include, but not be limited to, materials, quality control, testing, energy (expressed in terms of kilo watt hours), and waste treatment.
4. Clear identification of the assumptions made in the estimates.

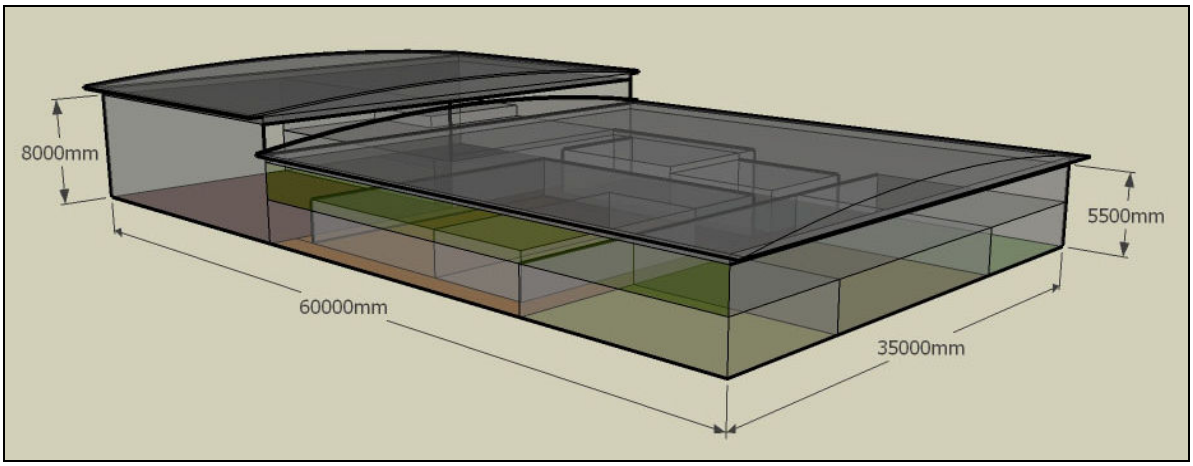
It should be noted that a fundamental assumption, for the purposes of this costing exercise only, is that the factories will only be operational for a maximum 3 month period following the opium harvest. In practice, it is strongly recommended that, in order to keep the factories operating during the remainder of the year, additional suitable products be identified and that these be manufactured using the same equipment.

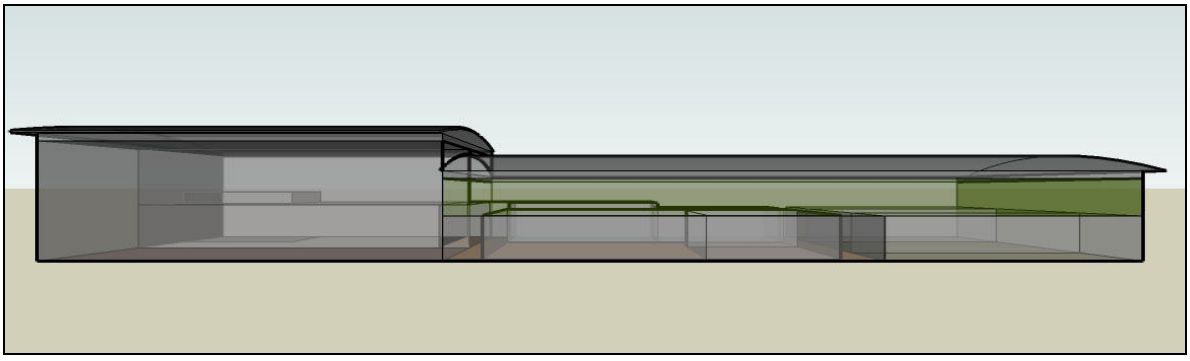
For illustrative and calculation purposes only, indicative drawings, both plan and 3-Dimensional of what each factory might look like have been prepared. These have been used to assist in the developing of the operational costings and should not be taken as representative of the appearance or layout of the final buildings. The drawings are as on the following pages:

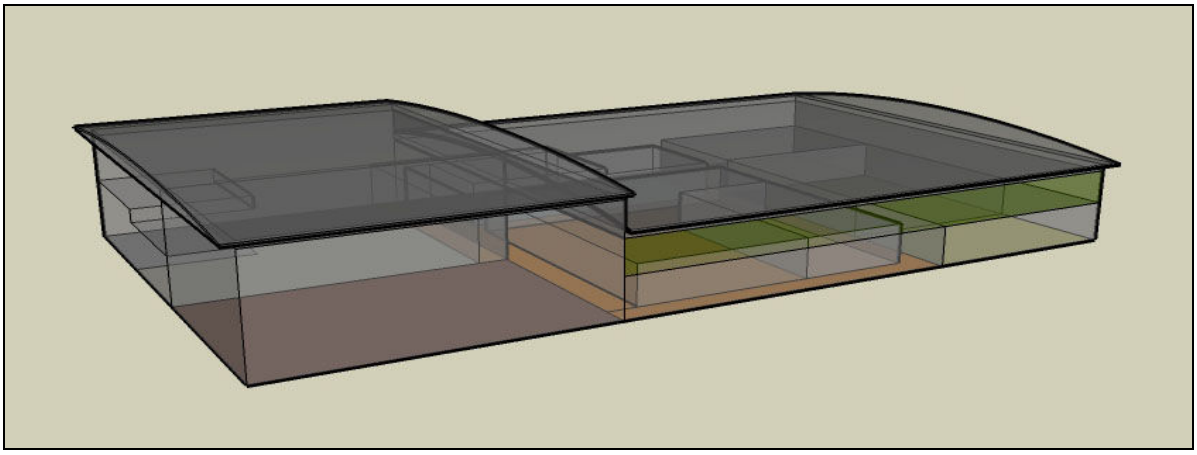
Indicative Block Layout:

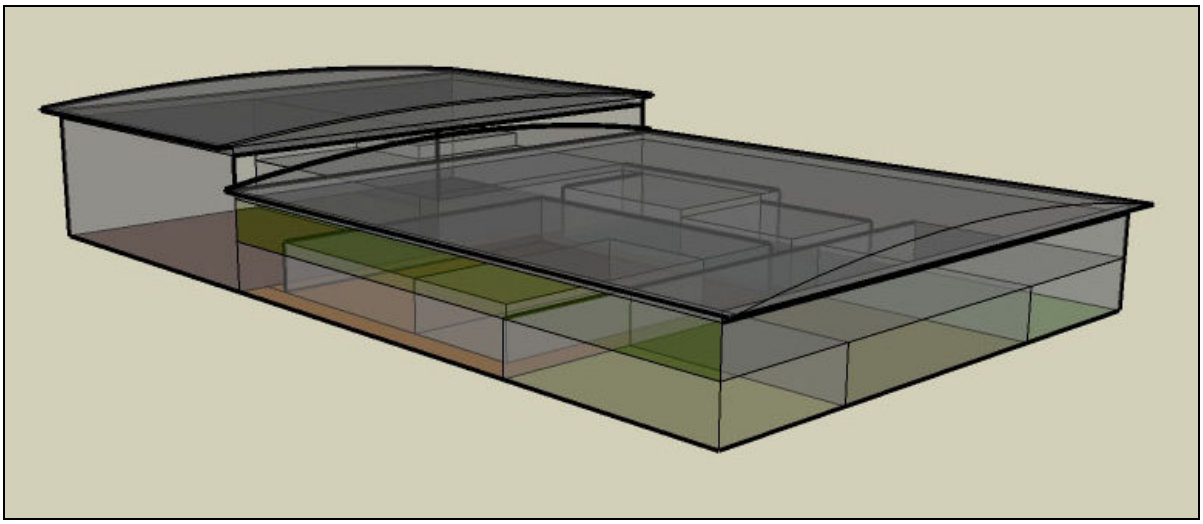


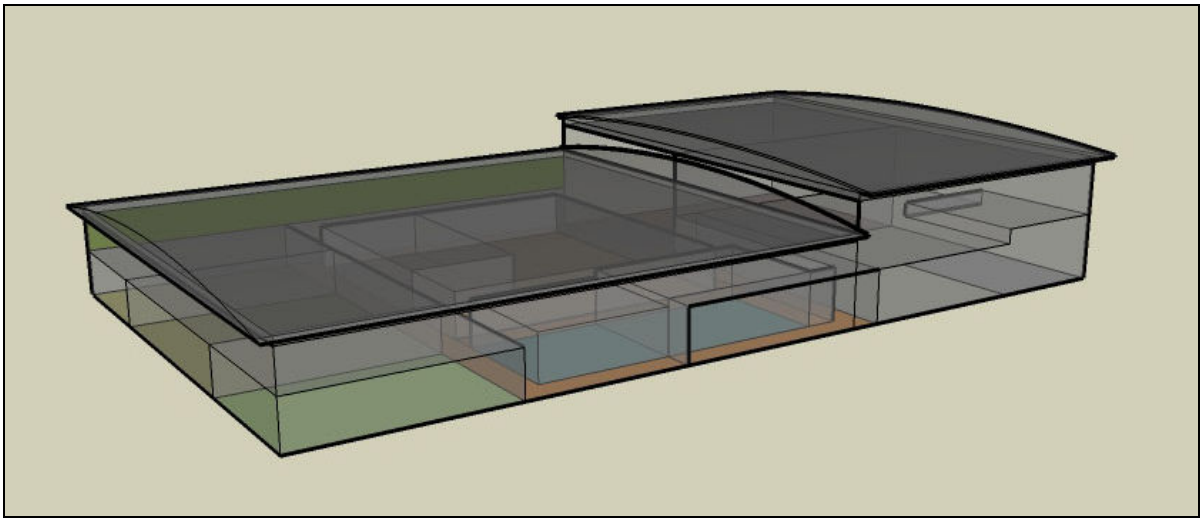
Indicative 3-D Block Layout











2. Prolonged Release Morphine Tablets

The brief from the The Senlis Council includes a potential requirement to manufacture prolonged release morphine tablets. For the control of intractable pain, and for treating cancer patients who rapidly develop tolerance to the normal low dose morphine preparations, it is desirable to have higher strength preparations that provide constant blood levels of the analgesic at all times. In some cases, these preparations contain quantities of morphine (e.g. 120 mg) that exceed the fatal dose in non-tolerant subjects.

The prolonged release preparations include both tablets and capsule presentations. The tablets include a wax matrix and various other types of slow release formulations, and are frequently coated to avoid the effect of stomach acid on the products. The capsule presentations are mostly hard-gelatine capsule shells enclosing pellets (non-pareil seeds) with various types of coating to provide controlled release of the morphine over, usually, a 12 hour period.

Each of these types of presentations requires specialised equipment for the manufacturing process. In the case of the tablets, various specialised granulation (mixing, granulating, and drying) equipment is required, and, in the case of capsules, either Wurster fluidised bed or perforated pan coating of the pellets is required. The tablets usually require film coating in perforated pans. The requirement for this specialised equipment necessitates larger manufacturing areas and much more expensive equipment.

It has been established that there are three prolonged release preparations on the UK market, and many more worldwide, that are now out of patent. However, the companies concerned continue to be the only ones manufacturing them, which, presumably, is due to the complex and highly secretive manufacturing processes. If it is decided that the new facilities are to manufacture prolonged release products, despite the initial capital cost and increased operational costs, then formal approaches may be made to these companies to try to obtain a licence to manufacture the products.

An alternative approach is to have a new product formulated and registered. An initial approach has been made to Azopharma, a company with divisions in France and the USA, and they have indicated a readiness to undertake the formulation and preparation of registration dossiers. For registration, assuming the product is identical to a branded version, the only clinical studies required will be bioavailability studies, so the entire process from start of formulation to completion of the registration dossier will only take about 6 months. However, there will be a substantial cost for this work; the total cost for this work is $237,500. The full quotation is included as Attachment 7.

It should be noted that the costs of development and registration will differ significantly depending on the selected markets. If, as previously stated, the principal markets will be in South America, where there are few patent restrictions, then the costs will be much lower than if the products are to be marketed in the USA and Western Europe. The quotation from Azopharma is made on this basis, and is for registration outside the USA and Europe. Before proceeding with a contract with a formulator, it will be necessary to define precisely where the products will and will not be marketed.

3. Analysis of Data – Schedules of Equipment and Areas for opium extraction and purification

3.1 Assumptions

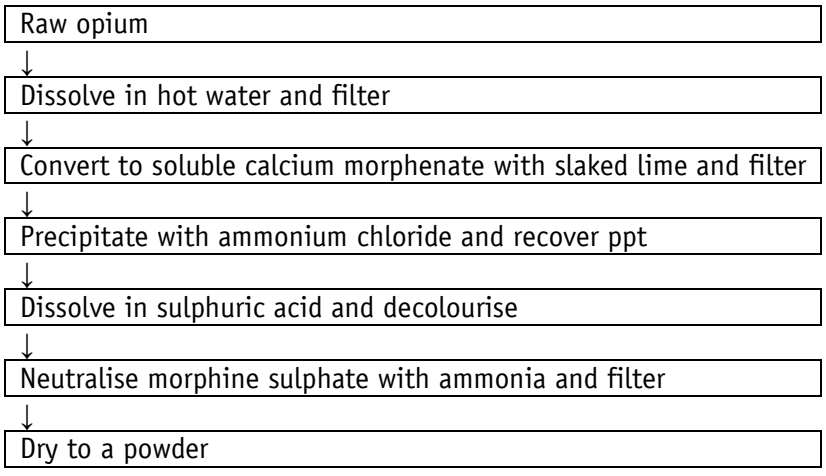
As the opium harvest season is relatively short, it is assumed that all of the extraction, processing, formulating, and packaging will be undertaken during a three month period. For the remainder of the year, each factory will either be closed down or will be used for the manufacture of other products.

All facilities will be designed and operated to international standards of pharmaceutical Good Manufacturing Practice (GMP). It is assumed that the products will be exported to countries demanding FDA and EU compliance standards, so the extraction and purification of the active pharmaceutical ingredient (API) will conform to ICH Q7 "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients."

3.2 Basic analysis

It is assumed that each manufacturing batch will require a cycle time of 1 week to prepare the facility, manufacture the product, and clean the equipment. Thus, a campaign will allow approximately 12 batches during the 3 month window. For convenience, it has been assumed that 10 batches will be processed, each consuming 100kg, 300kg, or 500kg of raw opium paste for each option 1 to 3 respectively. Each batch will therefore produce approximately 10kg, 30kg, and 50kg of refined morphine sulphate powder.

The refining process is summarised in the following flow diagram:



3.3 Performance Specifications

In order to minimise the narcotic effects of the raw material and product, it is proposed to contain all materials within closed equipment wherever possible. Where exposure is unavoidable, local extract ventilation will be required and operators will need to take precautions to avoid contact, ingestion, or inhalation.

Initial drying of the opium paste will be carried out in a tray drier. Either dry or wet opium may be dissolved in boiling water in a closed steam-heated vessel and filtered in an agitated Nutsche filter and transferred to another closed vessel. Each stage of the process described above will be performed by pumping from one vessel to another and back again through the Nutsche filter. When the volume reduces, separate smaller vessels will be used with a final small-scale bas filter. The size of each item of equipment depends on the scale of operation and is detailed below in the equipment schedule.

Final purified product will be dried in an enclosed fluid bed drier and filled into sealed drums directly from the bottom of the drier in order to minimise product exposure. All materials are delivered from the warehouse and weighed and prepared in the dispensary before utilisation in the manufacturing plant. In-process analysis such as checking moisture content and morphine content will be performed in an adjacent in-process control (IPC) laboratory. Quality Control (QC) of the bulk purified product will be performed in the central QC laboratory.
Utilities such as deionised water and plant steam are supplied from the central plant room.

3.4 Staffing

It is envisaged that the API facility will be operated by a single shift with typically the following staffing levels for each area.

Room	Operators	Supervisors
Extraction room	2	1
Drying room	1	
Dispensary/IPC lab	1	

4. Analysis of Data – Schedules of Equipment and Areas for production of morphine tablets

4.1 Assumptions

1. As the opium harvest season is relatively short, it is assumed that all of the extraction, processing, formulating, and packaging will be undertaken during a three month period. For the remainder of the year, each factory will either be closed down or will be used for the manufacture of other products.
2. The quantities of morphine sulphate available in the three factories will be 100kg, 300kg, and 500kg.
3. 100kg of morphine base will yield around 10 million tablets of 10mg morphine tablets, 3.5 million 30mg tablets, and 2 million 60mg tablets. If equal quantities are to be made of each strength of prolonged release product, the expected yield from 1 tonne of opium will be:

10 mg immediate release	0.9 million
10 mg prolonged release	0.9 million
30 mg prolonged release	0.9 million
60 mg prolonged release	0.9 million

   Thus the other two facilities, with opium quantities of 3 and 5 tonnes raw opium, will produce respectively 2.7 million of each strength and 4.5 million of each strength.
4. The prolonged release preparations may be either tablets or capsules. The equipment required for these two presentations is fundamentally different, but the space requirements will be similar. Both options are examined below.
5. If prolonged release tablets are the preferred option, it is assumed that these will be aqueous film coated.
6. If capsules are the preferred option, it is assumed that these will contain coated beads filled into hard-gelatine capsules.
7. Precise data on the packaging is not available at this time. Consequently, it has been assumed that the tablets will be packed into blisters of 30 tablets, and that two blisters, i.e. 60 tablets, will be packed into printed cartons. These cartons will be collated into bundles of 10, shrink-wrapped, and packed into shippers (outer cartons), placed on pallets, and stretch-wrapped for despatch and export.
8. All facilities will be designed and operated to international standards of GMP. It is assumed that the products will be exported to countries demanding Food and Drug Administration (FDA) and European Union (EU) compliance standards, so it will be essential to ensure that all aspects of the design, construction, equipment, validation, documentation, engineering, and operations are to full international GMP standards.

4.2 Basic analysis

As noted above, the three factories are to be designed to handle respectively 1, 3, and 5 tonnes of fresh opium paste. This is to be processed as follows:

- Dried to provide dry opium
- Morphine base is to be extracted from the dry opium
- The morphine is to be purified to produce pharmaceutical grade morphine sulphate powder.
- The morphine sulphate is to be formulated to produce tablets – 10mg immediate release tablets and 10mg, 30mg, and 60mg prolonged release tablets (or capsules).
- The finished tablets (and capsules) are to be packaged into blister packs for various export markets.

4.3 Performance Specifications

The slowest tablet press, using modern technology, will produce about 500-1000 tablets/minute, so, allowing 60% production efficiency, the total production time will be approximately 25 hours per annum per million for each strength, i.e. less than 3 weeks per annum for the smallest unit, rising to about 13 weeks for the largest.

If the facilities are only to be used for the production of morphine tablets, then they can be extremely simple units, with relatively little segregation between items of equipment. For the actual formulation of the tablets, it will be advisable to use the simplest technology, particularly for the immediate release tablets: this will use direct compression systems (DC), employing excipients such as DC lactose and DC starch. This will avoid the necessity for wet granulation and drying, both of which are space and energy consuming, and which will considerably increase the capital cost of the equipment.

The immediate release tablets are simple uncoated preparations. Thus, the equipment required for the tablet manufacture will comprise:

Warehouse

- Goods receiving
- Raw materials secure storage (opium paste & morphine sulphate)
- Raw materials non-secure storage (excipients & reagents)
- Packaging components – secure for printed and non-secure for unprinted
- Finished goods secure storage

Dispensary:*

- Downflow booth 2m width, with materials airlock
- Pit-mounted floor balance for up to 300kg

– Table-top balance for up to 10kg

– Vibratory sieve

Blending

– IBC blender (100 kg, 300 litres)

– IBC 300 litre x 4

Compressing

– Tablet press 500-1000/hr B-tooling

– De-duster

– Metal detector

* N.B. In view of the low volume of materials being dispensed, it is recommended that the dispensary downflow booth also be used for raw material sampling.

If prolonged release products are to be manufactured, then there will be the following alternative additional equipment:

1. Tablets, using matrix:

– High shear mixer – 100kg working capacity

– Sizing mill (Comil) – 200kg per hour working capacity

– Fluid bed dryer – 100kg working capacity

– Film coater – 100kg working capacity

2. Capsules containing coated beads

– Wurster coater for coating beads – 100kg working capacity

– Capsule filler and polisher/de-duster – 25-30,000 per hour

IPC Laboratory

– Tablet hardness tester

– Uniformity of weight tester

– Disintegration tester

– Friability tester

– Dimension testing equipment

QC Laboratory

– Dissolution testing equipment

– HPLC

– UV Spectrophotometer

– Near IR

Packing:

- Blister packer to pack 20 blisters of 30 tablets per minute. Blister packer to have in-line foil printing to print variable data in two colours. Embossed batch and expiry date coding to be provided.
- Packing table for cartoning 2 blisters per carton. Table to be large enough for 4 operators.
- Stand-alone shrink wrapper, capable of shrink-wrapping one bundle of 10 cartons per minute
- Manual stretch-wrap applicator for pallet wrapping.

4.4 Staffing

It is assumed that there will be both male and female staff throughout the facility. If this is not the case, then there will be a corresponding saving in duplication of changing and toilet facilities.

The number of staff required in the various areas will be as follows:

4.4.1 Without prolonged release product:

Department	Area	Number of staff	Classification
Warehouse, Goods Inwards, and Despatch		3 inc supervisor	Factory change
Manufacturing	Dispensary & Blending	2	Grade D
	Compression	2	Grade D
	Primary packaging	2	Grade D
Secondary Packaging		4	Factory Change
Production Manager		1	All
Quality Control	IPC laboratory	1	Grade D
	QC laboratory	2	Factory Change
Engineering		3 inc manager	Technical
Total		20	

It may be assumed that 12-15 of these will be female and that 5-8 will be male.

4.4.2 With prolonged release product:

Department	Area	Number of staff	Classification
Warehouse, Goods Inwards, and Despatch		3 inc supervisor	Factory change
Manufacturing	Dispensary & Blending	2	Grade D
	Compression & Coating	2	Grade D
	Granulation or Capsule Filling	2	Grade D
	Primary packaging	2	Grade D
Secondary Packaging		4	Factory Change
Production Manager		1	All
Quality Control	IPC laboratory	1	Grade D
	QC laboratory	2	Factory Change
Engineering		3 inc manager	Technical
Total		22	

The ratio of male to female staff will be similar to those in 4.4.1.

5. Equipment Costings

5.1 Opium paste extraction and purification: Capital Costs

Capital costs are calculated from recent equipment quotations from Indian equipment suppliers as detailed in the Appendix below. For each item of equipment, additional requirements comprising pipework, process controllers, instrumentation, electrical starters and ancillary steelwork are estimated and included into the total cost per equipment item. The total comprises the "prime cost" as listed in the following table.

For each option, the prime cost is supplemented with an estimate of

- Indirect construction costs (4% for e.g. site setup),
- Professional services (30% for engineering, procurement, management, commissioning and validation)
- Escalation (2% to cover prices rises since the date of the quotation)
- Contingency at 20% to cover uncertainties in scope

Please note: The addition of the above costs on top of the basic equipment cost is different to the costing method used for the secondary production area and is a result of the more extensive requirement for engineering and management in an API facility and a more complex approach to commissioning and validation.

Option 1	Prime cost £	Construction Indirects £	Professional Services £	Escalation £	Contingency £	Total £
Process	158,550	6,342	49,468	4,287	43,729	262,376
Utilities	0	0	0	0	0	0
Total	158,550	6,342	49,468	4,287	43,729	**262,376**

Option 2	Prime cost £	Construction Indirects £	Professional Services £	Escalation £	Contingency £	Total £
Process	210,100	8,404	65,551	5,681	57,947	347,684
Utilities	0	0	0	0	0	0
Total	210,100	8,404	65,551	5,681	57,947	**347,684**

Option 3	Prime cost £	Construction Indirects £	Professional Services £	Escalation £	Contingency £	Total £
Process	250,000	10,000	78,000	6,760	68,952	413,712
Utilities	0	0	0	0	0	0
Total	250,000	10,000	78,000	6,760	68,952	**413,712**

5.2 Opium paste extraction and purification: Operating Costs

The principal raw material is raw opium, which according to the Poppy for Medicine Technical Dossier published by the Senlis Council will be costed at around $140/kg The remaining raw materials are costed from the Sigma-Aldrich catalogue for India that conform reasonably closely to the costs suggested in the Morphine Manufacturing Flow Chart. An additional allowance of 20% of non-opium costs is included for unidentified materials and consumables.

Utilities are not included in the cost of API. Consumption will be included elsewhere. Depreciation of process equipment would normally be calculated over an equipment lifetime of 10 years, but is not included here.

Option 1 API	Cost per batch £	Kg/batch	Cost £/kg morphine
Opium	7,000.00	10	700.00
Other materials	850.00	10	85.00
Total	7,850.00		785.00

Option 2 API	Cost per batch £	Kg/batch	Cost £/kg morphine
Opium	21,000.00	30	700.00
Other materials	2,551.00	30	85.00
Total	23,551.00		785.00

Option 3 API	Cost per batch £	Kg/batch	Cost £/kg morphine
Opium	35,000.00	50	700.00
Other materials	4,252.00	50	85.00
Total	39,252.00		785.00

5.3 Manufacture & Packaging of Morphine Tablets (Attachments 4 & 5)

All equipment costings are based on recent quotations. Those from Western Europe are from known reputable suppliers. Those from companies in the Far East are from Chinese and Indian suppliers. The quality and reliability of these items have not been fully investigated. With the vast price differences between European and Far Eastern suppliers, it is recommended that very thorough checks be undertaken before any orders are placed with the latter. However, the cost of these investigations would appear to be well justified.

It is known that a number of internationally known multi-national pharmaceutical companies, such as GlaxoSmithKline, have bought equipment from some of the suppliers approached for the current quotations.

Wherever possible, suppliers have been asked to quote for FOB prices, with full Installation Qualification (IQ)and Operational Qualification (OQ) documentation. Not all suppliers have included this, or the installation, commissioning, and training costs, so the contingency figure allows for an additional 10% for this. Another additional cost will be the CIF charges. For these, an additional 15% has been included. Thus, the contingency figure of 25% provides for the full supply, installation, commissioning, and IQ and OQ stages of qualification.

Attachment 4 is the spreadsheet for the equipment required for the manufacture of only immediate release tablets, i.e. no prolonged release products. The budget costs for equipment are as follows:

- Western European equipment: £ 909,375.00
- Far Eastern equipment: £ 402,875.00

Attachment 5 is the spreadsheet for the probable equipment required for the manufacture of prolonged release products, as well as the immediate release tablets:

- Western European equipment: £ 1,495,125.00
- Far Eastern equipment: £ 503,500.00

5.4 Additional Items

It should be noted that there is unlikely to be mains electrical supply in the areas where the factories are to be located. Consequently, it will be necessary to use diesel fuelled generators for the generation of electricity. It is estimated that two x 250kVA generators will be required to power each factory. It is recommended that each factory be provided with a stand-by unit of similar size.

The cost of the generators locally is reported to be approximately $60,000 each, so the cost for each factory will be $180,000, equivalent to approximately £90,000.
All other plant items are included in the facility costs in Section 6 of this report.

6. Facility Costings

6.1 Warehousing

The basic assumptions for this area are:

1. The open racking areas will be designed as 'Pharmaclean', with EU5 standard of filtration, and temperature maintained in the range 16-24^{0}C. There will be no humidity control.
2. The building height throughout will be approximately 8 metres, so the racking will be 5 pallets high. Consequently, only a standard reach truck will be required, with standard aisles throughout.
3. With a relatively low storage height, no special floor finishes or guides will be required.
4. There will be a secure store for opium paste, and for the purified morphine sulphate.
5. There will be a separate secure store for packed finished goods containing morphine sulphate.
6. Access to the warehouse will be via a single (in and out) windlock, with interlocked doors.
7. The warehouse staff will change in the general factory change area. There will be no separate change area for warehouse staff.
8. The warehouse areas have been sized the same for all three factories on the basis of similar inventory levels, the production being spread over a longer period of time for the 3 tonne and 5 tonne processing factories.

6.2 Opium Paste Extraction & Purification

The following assumptions have been made:

1. A separate dispensary is included for API materials.
2. Processing rooms (extraction, drying, dispensary, and clean corridor) will be designed and operated to Pharmaclean standards (i.e. F8 filtration) as the process will be operated using primary containment.
3. The room areas and heights for the API section are given in the attachment below. All processing rooms remain the same size regardless of the scale of operation.

Options 1 to 3

Classification	**Areas**	**Cost per m^2**	**Total Cost**
Grade D	40	£1500	£60,000
Pharmaclean – non-secure	142	£800	£145,600
Unclassified	75	£500	£89,750
Total	**257**		**£211,100**

6.3 Morphine Tablets Manufacture & Packaging

The basic assumptions for these areas are:

1. The dispensary will be used for raw material sampling as well as for weighing raw materials.
2. All areas in which the product is exposed, i.e. dispensary, manufacturing, and primary (blister) packaging, will be designed and operated to Grade D (EU) standards. As all manufacture and packaging will be undertaken on a campaign basis (should more than one product be manufactured), all air-conditioning will be on a recirculation basis. However, it will be necessary to fit high efficiency particluate air (HEPA) filtration in the return air due to the narcotic nature of the morphine.
3. The secondary packing areas (cartoning, shrink-wrapping, and packing in shippers) will be to Pharmaclean standards, i.e. F8 filtration.
4. All Grade D areas are to have the following basic standards:
   - 19-23^{0}C
   - 35-55 % RH
   - > 20 air changes per hour.
   - All air to be recirculated
   - >15% fresh air make-up
5. The Pharmaclean areas associated with manufacture and packaging (factory change area, secondary packaging) are to have similar temperature and humidity conditions, but the air change rate can be reduced to >10 per hour.
6. The building height overall, as noted above, will be approximately 8 metres. It is proposed that the air conditioning plant for these areas should be located on a mezzanine floor over the packaging areas, the space above the manufacturing being left as a void for ease of installation of ducting.
7. The ceiling heights throughout the manufacturing and packaging areas will be 2.8 metres, with the exception of the granulation (if required) and compression areas, each of which will have a ceiling height of 4 metres.

6.4 Quality Control Laboratory

The basic assumptions for these are:

1. There will be three areas within the laboratory suite
   - Wet chemistry and physical testing
   - Instrument laboratory
   - Write up area and office
2. The area will be operated to Pharmaclean standard, i.e. F8 filtration, with recirculated air (>15% fresh air make-up), and all conditions as in section 5.3.
3. There will be no microbiology activities.

4. Only a single fume cupboard will be required

6.5 Plant

The basic assumptions for these are:

1. There will be a steam boiler to generate process heating (if fluid bed drying and/or film coating is required). Heating for air-conditioning will be provided by a closed circuit low temperature hot water system using oil/gas-fired condensing boilers as the heat source.
2. Chilling will be provided by conventional cooling tower and chiller.
3. There will be a single air compressor, with dryer and filter, air being supplied via a conventional reservoir.
4. The plant area will include the Purified Water plant.
5. The plant area will be at ground level within the building shell.

6.6 Ancillary Areas – Engineering & Staff Amenities

These will include:

1. Engineering workshop
2. Canteen
3. Prayer room
4. First aid room
5. Training and meeting room
6. Administrative offices

6.7 Costings for Facility excluding Prolonged Release Products (see attached spreadsheet – Attachment 1)

It should be noted that the sizing and costing of the raw materials, packing components, and secure stores are based on these being shared between the API and the secondary manufacturing facilities. Although the storage requirements for the three sizes of facility (1 tonne, 3 tonnes, & 5 tonnes of opium paste) may vary slightly, for the benefit of this exercise a single size has been assumed for all three options, as the operational period will increase as the quantities handled increase, rather than the actual batch sizes changing.

These costings exclude the cost of the building shell, i.e. are the costs of internal fit-out and servicing only.

Classification	Areas	Cost per m^2	Total Cost
Grade D	340	1,500	510,000
Pharmaclean – non-secure	465	800	372,000
Pharmaclean – secure storage	110	1,000	110,000
Unclassified	670	500	335,000
Total	**1,585**		**1,327,000**

6.8 Costings for Facility <u>including</u> Prolonged Release Products (see attached spreadsheet – Attachment 2)

These costings also exclude the cost of the building shell:

Classification	Areas	Cost per m^2	Total Cost
Grade D	430	1,500	645,000
Pharmaclean – non-secure	465	800	372,000
Pharmaclean – secure storage	110	1,000	110,000
Unclassified	750	500	375,000
Total	**1,755**		**1,492,000**

7. Operational Costs

7.1 Basis of Calculations

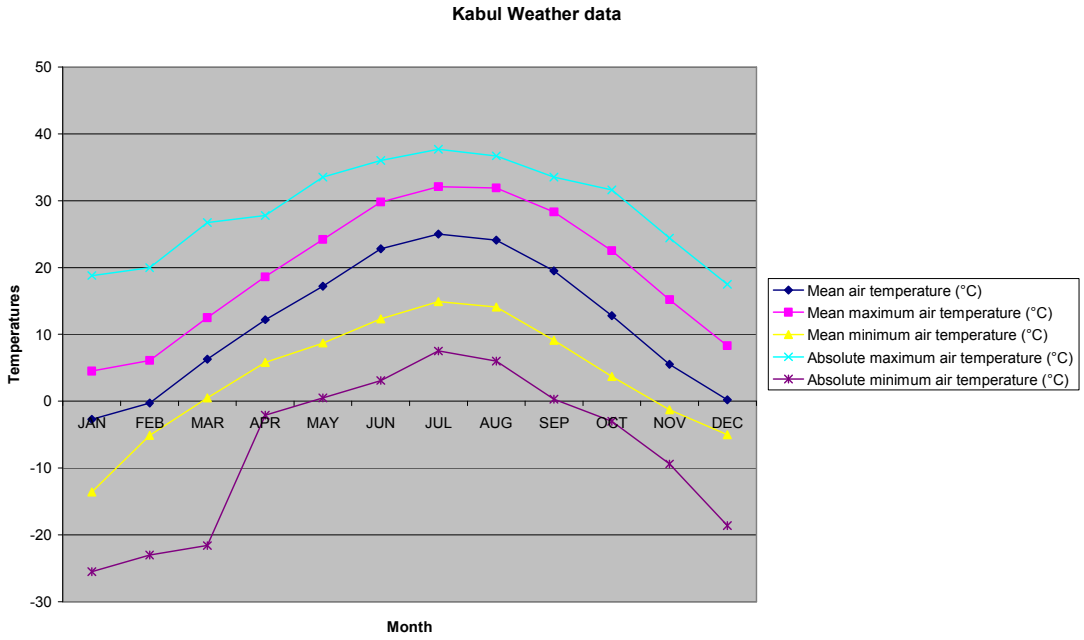
The operational costs have been estimated based on the areas of the processing and support rooms as scheduled in Attachments 1 and 3, and the space heights stated in Section 6.3 and in Attachment 3.

The external design conditions adopted for the heating ventilating and air conditioning (HVAC) equipment sizing calculations and for energy consumption calculations are:

- Summer: 30.5°C DB, 40%RH
- Winter: -11.1 °C DB 90%RH.

A temperature hourly climate model was constructed to conduct the energy calculations for this study. The model was based on climatic data from "M. Müller, 1983: Handbuch ausgewählter Klimastationen der Erde. Universität Trier. Forschungsstelle. Bodenerosion". No suitable data was found from conventionally used sources such as ASHRAE or CIBSE.

The temperature climate model was based on the monthly mean maximum and mean minimum temperatures as charted below.



The room environmental criteria used for the HVAC calculations are as stated for the space classification criteria in Sections 6.3 and 6.4. The individual space classifications used in the calculations are as in Attachments 2 and 3.

The processing equipment and utilities electrical demands and environmental gains used for the HVAC calculations and for the energy consumption calculations are those provided by the study team's process consultants.

The energy calculations have also been based on the premise stated in the Introduction to this report that the factories will be operate for a three month manufacturing campaign during and following the poppy harvest. For purposes of energy calculations, these months have been taken to be July, August, and, September. Again for purposes of energy calculations it has been assumed that the factories will be set back to a minimum of functionality and ventilation outside the manufacturing campaign.

For calculation purposes, a six day per week, nine hour per day, including mid-day break, operational shift pattern has been assumed during the manufacturing campaign. Non-essential plant setback has been applied in the calculations outside the operating shift hours for energy saving purposes.

7.2 Building Air Conditioning Plant

The performance parameters for the principal HVAC plant required to serve the factory has been calculated based on the design criteria above and are tabulated below:

Ref.	Item	Area Served	Equipment Location	Capacity	Units	Remarks	Absorbed Power kW
Air Systems							
Supply Air Systems							
AHU 1	Air Handling Unit	API Process & Clean Corridor	Roof Plantroom	4.836	m³/s	1 @ 100%	12.2
AHU 2	Air Handling Unit	API Cleaning & Black Corridor	Roof Plantroom	0.880	m³/s	1 @ 100%	2.2
AHU 3	Air Handling Unit	Administration	Roof Plantroom	1.679	m³/s	1 @ 100%	4.2
AHU 4	Air Handling Unit	Change areas	Roof Plantroom	0.856	m³/s	1 @ 100%	2.2
AHU 5	Air Handling Unit	Warehouse	Roof Plantroom	1.953	m³/s	1 @ 100%	4.9
AHU 6	Air Handling Unit	Secondary Manufacturing	Roof Plantroom	8.241	m³/s	1 @ 100%	20.9
AHU 7	Air Handling Unit	Secondary Packing	Roof Plantroom	1.008	m³/s	1 @ 100%	2.6
AHU 8	Air Handling Unit	QC Laboratories	Roof Plantroom	1.375	m³/s	1 @ 100%	3.5
Extract Air Systems							
AEU 1	Air Extract Unit	API Process & Clean Corridor	Roof Plantroom	4.836	m³/s	1 @ 100%	8.2
AEU 2	Air Extract Unit	API Cleaning & Black Corridor	Roof Plantroom	0.880	m³/s	1 @ 100%	1.5
AEU 3	Air Extract Unit	Administration	Roof Plantroom	1.679	m³/s	1 @ 100%	2.8
AEU 4	Air Extract Unit	Change areas	Roof Plantroom	0.856	m³/s	1 @ 100%	1.4
AEU 5	Air Extract Unit	Warehouse	Roof Plantroom	1.953	m³/s	1 @ 100%	3.3

Ref.	Item	Area Served	Equipment Location	Capacity	Units	Remarks	Absorbed Power kW
AEU 6	Air Extract Unit	Secondary Manufacturing	Roof Plantroom	8.241	m³/s	1 @ 100%	13.9
AEU 7	Air Extract Unit	Secondary Packing	Roof Plantroom	1.008	m³/s	1 @ 100%	1.7
AEU 8	Air Extract Unit	QC Laboratories	Roof Plantroom	1.375	m³/s	1 @ 100%	2.3
Ventilation Fans							
EF 01	Extract Fan	General plantroom extract	Roof Plantroom	4.500	m³/s		1.0
EF 02	Extract Fan	Laboratory extracts	Roof Plantroom	1.000	m³/s		0.3
EF 03	Extract Fan	Workshop extract	Roof Plantroom	0.500	m³/s		0.1
Hydronic Systems							
Heat Source							
B1	LTHW Boiler	Building Air Conditioning	Wet Plantroom	266.0	kW	2 @ 60%	5.0
B2	LTHW Boiler	Building Air Conditioning	Wet Plantroom	26.0	kW	2 @ 60%	5.0
P4	Chilled Water Pump	LTHW Boiler B1	Wet Plantroom	4,2	l/s	3 @ 100%	5.0
P5	Chilled Water Pump	LTHW Boiler B 2	Wet Plantroom	4,2	l/s	3 @ 100%	5.0
P6	Chilled Water Pump	LTHW Boiler Standby Pump	Wet Plantroom	4,2	l/s	3 @ 100%	5.0
Cooling Source							
WCC 01	Air/Water Cooled Chillers	Building Air Conditioning	Wet Plantroom	192.9	kW	2 @ 60%	80.0
WCC 02	Air/Water Cooled Chillers	Building Air Conditioning	Wet Plantroom	192.9	kW	2 @ 60%	80.0
CT 01	Cooling Tower	Building Air Conditioning	External			2 @ 60%	15.0
CT 02	Cooling Tower	Building Air Conditioning	External			2 @ 60%	15.0
P1	Chilled Water Pump	Chiller WCC 01	Wet Plantroom	7.7	l/s	3 @ 100%	7.0
P2	Chilled Water Pump	Chiller WCC 02	Wet Plantroom	7.7	l/s	3 @ 100%	7.0
P3	Chilled Water Pump	Chilled Water Standby Pump	Wet Plantroom	7.7	l/s	3 @ 100%	7.0

In order to take advantage of the large range of extremes of external temperatures, it is proposed that the chilled water cooling source for the building air conditioning system comprise direct expansion water chillers with closed refrigerant circuit cooling towers. These are to be arranged for evaporative forced convection heat rejection in the hot season, and for dry forced convection heat rejection in intermediate and cold seasons.

There is a lack of water distribution infrastructure. It is therefore probable that a consideration for locating the factory sites will be the availability of underground aquifers to provide borehole water sources, together with on-site water storage and primary treatment, if necessary. There is a cost and energy balance between the issues of water requirements and of

chilled water system energy consumption, depending on the heat rejection technology implemented. This is beyond the scope of this study.

Similarly, for energy efficiency reasons, it is proposed that steam heating be provided for process use only, and that the heating requirements for the air conditioning, such as heating coils and re-heat coils, be provided by a closed circuit low temperature hot water system using oil/gas-fired condensing boilers as the heat source.

7.3 Building Electrical Plant

The installed capacity of the electrical plant has been based on the process and HVAC equipment plant data, and on the requirements for lighting and general power to suit conventional criteria for pharmaceutical manufacturing factories.

The availability of electricity from the National Grid in Afghanistan is not universal, nor is it dependable. It will be necessary to provide full generation capacity for each of the factories. In addition, the fuel is generally shipped overland by tanker from Pakistan. It is therefore common practice to provide on-site fuel storage for all the site requirements.

The quality of the imported fuel is not high, and the local operating conditions are onerous leading to considerable downtime on the electrical generation plant. It is advisable to provide 100% standby generation to allow for these factors.

The calculated connected load for the factory is = 513 kW.
The maximum demand is estimated as = 427 kW.

7.4 Energy Operational Costs

- The estimated annual energy consumption for electrical loads = 746 MWh/annum
- The generator fuel consumption for the load= 127,400 litres/annum
- The estimated annual energy consumption for heating boilers = 183MWh/annum
- The fuel consumption for the boiler load = 24,300 litres/annum
- The total site annual fuel demand = 151,700 litres/annum
- At approximately US$1.4 (£0.70) per litre fuel cost, the annual energy cost is estimated at US$212,380/annum (£106,000).

8. Conclusions and Recommendations

From the previous sections, it can be seen that the costs of establishing a single opium processing factory in Afghanistan is going to be at least £2.0 million, excluding the costs of building the actual factory shell, and establishing the local infrastructure. Additional to these costs are going to be the professional fees for design, project management, and validation, as well as the costs of preparing all of the necessary quality assurance (QA), engineering, and operational documentation and systems. There will be additional costs involved in the recruitment and training of the necessary qualified staff, which is likely to present considerable problems given the dangerous territory in which the factories are to be established. Given all the necessary additional costs during the design, construction, and start-up, it is unlikely that the initial budget could or should be lower than £2.4 million (approximately $4.8 million). These figures are based on purchasing equipment manufactured in the Far East (India, Thailand, and China) rather than European equipment, there being at least a three-times price differential.

If the option of having a factory capable of producing prolonged release tablets or capsules is selected, there will be additional costs of approximately £200,000 ($400,000). Additionally, there will be the costs of developing the necessary formulations and registration of these in the selected markets: the cost of these will be at least $240,000 (£120,000). It is apparent that the majority of the world market, particularly for the relief of cancer pain, is for prolonged release products. Consequently, it would appear that it would be necessary for the factories to produce this type of product if it is to become a substantial and profitable company operating in the global market.

The operational costs, partly due to any pharmaceutical operation requiring a minimum of space, whatever the throughput, and partly due to the local climatic conditions, will be high, with the energy consumption alone being 746 MWh/annum. As indicated in Section 7, the likely cost of this will be in excess of £105,000 per annum.

It is suggested that the minimum production would need to be in excess of 20 million tablets or capsules. As the usual strength of prolonged release morphine tablets or capsules is 50mg or stronger, this would require at least 10 tonnes of opium paste. Consequently, whilst the plants could later be expanded to provide facilities for the manufacture of these products, it is suggested that this aspect of the project should be left in abeyance pending a substantial increase in the weight of opium to be processed.

Attachment 1 – Secondary Manufacturing Schedule of Areas without Prolonged Release Product

Area/Floor	Room	Classification	Area per room	No. of rooms	Total area m^2	Sub-total m^2
Change areas	Lobby	Unclassified	10	1	10	
	Male factory change	Pharma clean	20	1	20	
	Male ablutions	Pharma clean	20	1	20	
	Female factory change	Pharma clean	30	1	30	
	Female ablutions	Pharma clean	20	1	20	
	Male manufacturing change	Grade D	15	1	15	
	Female manufacturing change	Grade D	15	1	15	130
Materials warehouse	Goods receiving	Unclassified	30	1	30	
	Office/WC	Unclassified	15	1	15	
	Racked storage - RM & PC	Pharma clean	150	1	150	
	Re-palletisation area	Pharma clean	20	1	20	
	Secure store - raw materials	Pharma clean	50	1	50	
	Secure store - finished goods	Pharma clean	60	1	60	
	Shelved storage	Pharma clean	20	1	20	345
Dispensary	Staging area	Grade D	25	1	25	
	Downflow booth	Grade D	15	1	15	
	Consumables store	Grade D	5	1	5	
	Wash area	Grade D	10	1	10	
	Bench stock store	Grade D	10	1	10	
	Circulation & Office (30%)	Grade D	35		35	100
Blending	Blending cubicle	Grade D	20	1	20	
IBC Washing		Grade D	30	1	30	50
Compression	Compression booth inc pillar lift	Grade D	20	1	20	
	Tooling store & workshop	Grade D	20	1	20	
	In-process laboratory	Grade D	15	1	15	
	Wash area	Grade D	15	1	15	
	Tablet bin washing	Grade D	10	1	10	
	Circulation (30%)	Grade D	30		30	110

Area/Floor	Room	Classification	Area per room	No. of rooms	Total area m^2	Sub-total m^2
Administration	Offices	Grade D	10	1	10	10
	Administration offices	Unclassified	10	3	30	
	Training room	Unclassified	40	1	40	
	Tea room & kitchen	Unclassified	40	1	40	
	Cleaners store	Unclassified	10	1	10	
	First Aid room	Unclassified	15	1	15	
	Prayer room	Unclassified	20	1	20	
	Engineering workshop	Unclassified	30	1	30	185
Packing	Staging	Grade D	10	1	10	
	Primary packing	Grade D	30	1	30	40
	Secondary packing	Pharma clean	50	1	50	
	Office, store, and circulation	Pharma clean	20		20	
	Bin & pallet storage	Pharma clean	15	1	15	85
Plant area	Energy centre	Unclassified	100	1	100	
	Purified water plant	Unclassified	30	1	30	
	Technical area	Unclassified	300	1	300	430
QC Laboratories		Pharmaclean	100		100	100

Areas	Grade D	340
	Pharmaclean non-secure	465
	Pharmaclean secure	110
	Unclassified	670
	Total	**1,585**

Attachment 2 – Secondary Manufacturing Schedule of Areas with Prolonged Release Product

Area/Floor	Room	Classification	Area per room m^2	No. of rooms	Total area m^2	Sub-total m^2
Change areas	Lobby	Unclassified	10	1	10	
	Male factory change	Pharma clean	20	1	20	
	Male ablutions	Pharma clean	20	1	20	
	Female factory change	Pharma clean	30	1	30	
	Female ablutions	Pharma clean	20	1	20	
	Male manufacturing change	Grade D	15	1	15	
	Female manufacturing change	Grade D	15	1	15	130
Materials warehouse	Goods receiving	Unclassified	30	1	30	
	Office/WC	Unclassified	15	1	15	
	Racked storage - RM & PC	Pharma clean	150	1	150	
	Re-palletisation area	Pharma clean	20	1	20	
	Secure store - raw materials	Pharma clean	50	1	50	
	Secure store - finished goods	Pharma clean	60	1	60	
	Shelved storage	Pharma clean	20	1	20	345
Dispensary	Staging area	Grade D	25	1	25	
	Downflow booth	Grade D	15	1	15	
	Consumables store	Grade D	5	1	5	
	Wash area	Grade D	10	1	10	
	Bench stock store	Grade D	10	1	10	
	Circulation & Office (30%)	Grade D	35		35	100
Granulation/Bead coating	Mixing, drying, and sizing/Bead Coating	Grade D	40	1	40	
	WIP	Grade D	20	1	20	60
Blending	Blending cubicle	Grade D	20	1	20	
IBC Washing		Grade D	30	1	30	50

Area/Floor	Room	Classification	Area per room m^2	No. of rooms	Total area m^2	Sub-total m^2
Compression/Capsule filling/Coating	Compression booth inc pillar lift	Grade D	20	1	20	
	Capsule filling/Tablet Coating	Grade D	30	1	30	
	Tooling store & workshop	Grade D	20	1	20	
	In-process laboratory	Grade D	15	1	15	
	Wash area	Grade D	15	1	15	
	Tablet bin washing	Grade D	10	1	10	
	Circulation (30%)	Grade D	30		30	140
Administration	Offices	Grade D	10	1	10	10
	Administration offices	Unclassified	10	3	30	
	Training room	Unclassified	40	1	40	
	Tea room & kitchen	Unclassified	40	1	40	
	Cleaners store	Unclassified	10	1	10	
	First Aid room	Unclassified	15	1	15	
	Engineering workshop	Unclassified	30	1	30	165
Packing	Staging	Grade D	10	1	10	
	Primary packing	Grade D	30	1	30	40
	Secondary packing	Pharma clean	50	1	50	
	Office, store, and circulation	Pharma clean	20		20	
	Bin & pallet storage	Pharma clean	15	1	15	85
Plant area	Energy centre	Unclassified	100	1	100	
	Purified water plant	Unclassified	30	1	30	
	Technical area	Unclassified	400	1	400	530
QC Laboratories		Pharmaclean	100		100	100

Areas	Grade D	430
	Pharma clean – non-secure	465
	Pharma clean - secure	110
	Unclassified	750
	Total	**1,755**

Attachment 3 – Schedule of Areas for API Manufacture

Area/Floor	**Room**	**Classification**	**Area per room m²**	**Room height m**	**Operators**	**Supervisors**
API Manufacturing	Extraction room	CNC	84.0	>3.5	2	
	Drying room	CNC	40.0	>2.5	1	1
	Dispensary/IPC lab	CNC	30.0	>2.5	1	
	Clean corridor	CNC	24.0	>2.5		
	Airlock	CNC	4.0	>2.5		
	Black corridor	NC	75.0	>2.5		
Additional to 2nd ary	Plant room	NC	84.0	>4.5	1	
	Total		**341.0**			

Attachment 4 – Equipment Costings without Prolonged Release Products

AREA	EQUIPMENT NAME	POSSIBLE SUPPLIERS	NO.	PRICE PER UNIT (Europe)	TOTAL PRICE (Europe)	PRICE PER UNIT (Far East)	TOTAL PRICE (Far East)
Dispensary	Proprietary Dust Control Booth	Extract Technology	1	£ 30,000.00	£ 30,000.00	£ 10,000.00	£ 10,000.00
	S/S Hand Pallet Truck	Syspal	1	£ 1,000.00	£ 1,000.00	£ 500.00	£ 500.00
	Platform Balance	Mettler, Sartorius, Stevens	1	£ 6,000.00	£ 6,000.00	£ 2,000.00	£ 2,000.00
	Bench-top Balance	Mettler, Sartorius, Stevens	1	£ 3,000.00	£ 3,000.00	£ 1,000.00	£ 1,000.00
	Bench Stock Bins	Pharmatech Equipment, Adelphi	5	£ 200.00	£ 1,000.00	£ 100.00	£ 500.00
	Vibratory Sieve	Russell Finex	1	£ 10,000.00	£ 10,000.00	£ 3,000.00	£ 3,000.00
	Scoops, S/S Containers,etc.	Pharmatech Equipment, Adelphi			£ 1,000.00	£ 500.00	£ 500.00
IBC system	IBCs 300 litres (drums)	Matcon, Glatt, GEA	4	£ 2,800.00	£ 11,200.00	£ 1,500.00	£ 6,000.00
	Tumble Blender	Matcon, Glatt, GEA	1	£ 27,000.00	£ 27,000.00	£ 10,000.00	£ 10,000.00
	IBC Wash & Dry Station	Matcon, Glatt, GEA	1	£ 12,000.00	£ 12,000.00	£ 4,000.00	£ 4,000.00
	Compression discharge stations	Matcon, Glatt, GEA	1	£ 9,200.00	£ 9,200.00	£ 3,000.00	£ 3,000.00
	S/S Pallet Truck		1	£ 1,000.00	£ 1,000.00	£ 500.00	£ 500.00
Compression	Single-sided press	IMA Kilian	1	£ 133,000.00	£ 133,000.00	£ 14,000.00	£ 14,000.00
	Deduster	Manesty	1	£ 18,000.00	£ 18,000.00	£ 2,100.00	£ 2,100.00
	Metal Detector	Lock	1	£ 4,000.00	£ 4,000.00	£ 1,500.00	£ 1,500.00
	S/S Pallet Truck	Syspal	1		£ 1,000.00	£ 500.00	£ 500.00
	Tooling	Holland	2 sets	£ 800.00	£ 1,600.00	£ 300.00	£ 600.00
	Tooling Maintenance Equipment	Holland	1	£ 5,000.00	£ 5,000.00	£ 5,000.00	£ 5,000.00
	Tooling Storage Cabinet	Holland	1	£ 1,000.00	£ 1,000.00	£ 1,000.00	£ 1,000.00
	Tablet Collection Bins (15kg)		40	£ 15.00	£ 600.00	£ 7.50	£ 300.00

AREA	EQUIPMENT NAME	POSSIBLE SUPPLIERS	NO.	PRICE PER UNIT (Europe)	TOTAL PRICE (Europe)	PRICE PER UNIT (Far East)	TOTAL PRICE (Far East)
IPC Laboratory	Uniformity of Weight Tester	Mettler, Sartorius	1	£ 8,000.00	£ 8,000.00	£ 3,000.00	£ 3,000.00
	Hardness Tester	Caleva	1	£ 4,000.00	£ 4,000.00	£ 1,500.00	£ 1,500.00
	Balance	Mettler, Sartorius	1	£ 3,000.00	£ 3,000.00	£ 1,000.00	£ 1,000.00
	Friability Tester	Caleva	1	£ 2,100.00	£ 2,100.00	£ 800.00	£ 800.00
	Disintegration Tester	Caleva	1	£ 3,800.00	£ 3,800.00	£ 1,500.00	£ 1,500.00
Packaging	Blister packer	IMA	1	£ 67,000.00	£ 67,000.00	£ 67,000.00	£ 67,000.00
	Shrink Wrapper	Erapa	1	£ 2,000.00	£ 2,000.00	£ 2,000.00	£ 2,000.00
Materials handling and storage	Stainless steel/aluminium pallets	Syspal	50	£ 100.00	£ 5,000.00	£ 50.00	£ 2,500.00
	Cage pallets - stainless steel	Syspal	10	£ 400.00	£ 4,000.00	£ 200.00	£ 2,000.00
	Fork Lift Truck	Crown, Toyota	1	£ 20,000.00	£ 20,000.00	£ 10,000.00	£ 10,000.00
	Reach Truck	Crown, Toyota	1	£ 40,000.00	£ 40,000.00	£ 20,000.00	£ 20,000.00
QC Laboratory	Dissolution tester	Caleva	1	£ 8,000.00	£ 8,000.00	£ 8,000.00	£ 8,000.00
	HPLC		1	£ 30,000.00	£ 30,000.00	£ 19,000.00	£ 19,000.00
	UV Spectrophotometer		1	£ 8,000.00	£ 8,000.00	£ 8,000.00	£ 8,000.00
	Near IR		1	£ 28,000.00	£ 28,000.00	£ 12,000.00	£ 12,000.00
	Miscellaneous			£ 50,000.00	£ 50,000.00	£ 20,000.00	£ 20,000.00
Miscellaneous	Filter washing machine	Electrolux	1	£ 8,000.00	£ 8,000.00	£ 3,000.00	£ 3,000.00
	Workshop tools			£ 50,000.00	£ 50,000.00	£ 15,000.00	£ 15,000.00
	Sundries			£ 50,000.00	£ 50,000.00	£ 20,000.00	£ 20,000.00
Specialised utility	Purified Water System	Veolia	1	£ 60,000.00	£ 60,000.00	£ 30,000.00	£ 30,000.00
Totals					£ 727,500.00		£ 322,300.00
Contingency 25%					£ 181,875.00		£ 80,575.00
Total, including contingency					**£ 909,375.00**		**£ 402,875.00**

Attachment 5 – Equipment Costings with Prolonged Release Product

AREA	EQUIPMENT NAME	POSSIBLE SUPPLIERS	NO	UNIT PRICE (Europe)	TOTAL PRICE (Europe)	UNIT PRICE (Far East)	TOTAL PRICE (Far East)
Dispensary	Proprietary Dust Control Booth	Extract Technology	1	£ 30,000.00	£ 30,000.00	£ 10,000.00	£ 10,000.00
	S/S Hand Pallet Truck	Syspal	1	£ 1,000.00	£ 1,000.00	£ 500.00	£ 500.00
	Platform Balance	Mettler, Sartorius, Stevens	1	£ 6,000.00	£ 6,000.00	£ 2,000.00	£ 2,000.00
	Bench-top Balance	Mettler, Sartorius, Stevens	1	£ 3,000.00	£ 3,000.00	£ 1,000.00	£ 1,000.00
	Bench Stock Bins	Pharmatech Equipment, Adelphi	5	£ 200.00	£ 1,000.00	£ 100.00	£ 500.00
	Vibratory Sieve	Russell Finex	1	£ 10,000.00	£ 10,000.00	£ 3,000.00	£ 3,000.00
	Scoops, S/S Containers,etc.	Pharmatech Equipment, Adelphi			£ 1,000.00	£ 500.00	£ 500.00
Granulation	High speed Mixer Granulator 250 litre	Aeromatic, Glatt	1	£ 80,000.00	£ 80,000.00	£ 22,000.00	£ 22,000.00
	Fluid bed dryer 250 litre	Aeromatic, Glatt	1	£ 150,000.00	£ 150,000.00	£ 25,000.00	£ 25,000.00
	Wet mill	Ytron Quadro	1	£ 18,000.00	£ 18,000.00	£ 6,000.00	£ 6,000.00
	Sizing mill	Ytron Quadro	1	£ 18,000.00	£ 18,000.00	£ 6,000.00	£ 6,000.00
Compression	Single-sided press	IMA Kilian	1	£ 133,000.00	£ 133,000.00	£ 14,000.00	£ 14,000.00
	Deduster	Manesty	1	£ 18,000.00	£ 18,000.00	£ 2,100.00	£ 2,100.00
	Metal Detector	Lock	1	£ 4,000.00	£ 4,000.00	£ 1,500.00	£ 1,500.00
	S/S Pallet Truck	Syspal	1		£ 1,000.00	£ 500.00	£ 500.00
	Tooling	Holland	2 sets	£ 800.00	£ 1,600.00	£ 300.00	£ 600.00
	Tooling Maintenance Equipment	Holland	1	£ 5,000.00	£ 5,000.00	£ 5,000.00	£ 5,000.00
	Tooling Storage Cabinet	Holland	1	£ 1,000.00	£ 1,000.00	£ 1,000.00	£ 1,000.00
	Tablet Collection Bins (15kg)		40	£ 15.00	£ 600.00	£ 7.50	£ 300.00
Coating	Coating pan 400L Ex'd	Manesty. Thai Coater	1		£ 263,000.00	£ 55,000.00	£ 55,000.00
Packaging	Blister Packing Line	IMA	1	£ 67,000.00	£ 67,000.00	£ 67,000.00	£ 67,000.00
	Shrink Wrapper	Erapa	1	£ 2,000.00	£ 2,000.00	2000	£ 2,000.00

AREA	EQUIPMENT NAME	POSSIBLE SUPPLIERS	NO	UNIT PRICE (Europe)	TOTAL PRICE (Europe)	UNIT PRICE (Far East)	TOTAL PRICE (Far East)
IPC Laboratory	Uniformity of Weight Tester	Mettler, Sartorius	1	£8,000.00	£8,000.00	£3,000.00	£3,000.00
	Hardness Tester	Caleva	1	£4,000.00	£4,000.00	£1,500.00	£1,500.00
	Balance	Mettler, Sartorius	1	£3,000.00	£3,000.00	£1,000.00	£1,000.00
	Friability Tester	Caleva	1	£2,100.00	£2,100.00	£800.00	£800.00
	Disintegration Tester	Caleva	1	£3,800.00	£3,800.00	£1,500.00	£1,500.00
Materials handling and storage	Stainless steel/aluminium pallets	Syspal	50	£100.00	£5,000.00	£50.00	£2,500.00
	Cage pallets - stainless steel	Syspal	10	£400.00	£4,000.00	£200.00	£2,000.00
	Fork Lift Truck	Crown, Toyota	1	£20,000.00	£20,000.00	£10,000.00	£10,000.00
	Reach Truck	Crown, Toyota	1	£40,000.00	£40,000.00	£20,000.00	£20,000.00
QC Laboratory	Dissolution tester	Caleva	1	£8,000.00	£8,000.00	£8,000.00	£8,000.00
	HPLC	Waters	1	£30,000.00	£30,000.00	£19,000.00	£19,000.00
	UV Spectrophotometer		1	£8,000.00	£8,000.00	£8,000.00	£8,000.00
	Near IR		1	£28,000.00	£28,000.00	£12,000.00	£12,000.00
	Miscellaneous			£50,000.00	£50,000.00	£20,000.00	£20,000.00
Miscellaneous	Filter washing machine	Electrolux	1	£8,000.00	£8,000.00	£3,000.00	£3,000.00
	Workshop tools			£50,000.00	£50,000.00	£15,000.00	£15,000.00
	Sundries			£50,000.00	£50,000.00	£20,000.00	£20,000.00
Specialised utility	Purified Water System	Veolia	1	£60,000.00	£60,000.00	£30,000.00	£30,000.00
Totals					£1,196,100.00		£402,800.00
Contingency 25%					£299,025.00		£100,700.00
Total, including contingency					**1,495,125.00**		**£503,500.00**

Attachment 6a – API Equipment Costings Option 1

AREA	EQUIPMENT NAME	POSSIBLE SUPPLIERS	NO	UNIT PRICE (India)	Ancillaries (piping, electrics etc)	TOTAL PRICE (Far East)
Dispensary	Dust Control Booth	Extract Technology	1	£10,000	£650.00	£10,650.00
	S/S Hand Pallet Truck	Syspal	1	£500	£0.00	£500.00
	Platform Balance	Mettler, Sartorius, Stevens	1	£2,000	£650.00	£2,650.00
	Bench-top Balance	Mettler, Sartorius, Stevens	1	£1,000	£0.00	£1,000.00
	Bench Stock Bins	Pharmatech Equipment, Adelphi	3	£100	£0.00	£100.00
IPC lab	Moisture test/balance		1	£2,000	£650.00	£2,650.00
	Spectrophotometer		1	£8000	£650.00	£8,650.00
Pre-drying	Tray drier	Wintech tray drier 12 trays	1	£10,000	£2,150.00	£12,150.00
Process room	Drum lifter		1	£2,000	£0.00	£2,000.00
	Jacketed tank 1 400L	SS jacketed IDMC	1	£7,000	£10,100.00	£17,100.00
	Agitator 1		1	£3,400	£1,250.00	£4,650.00
	Pump 1		1	£1,000	£3,650.00	£4,650.00
	Large filtration system	ChemPro 0.25m	1	£15,000	£5,750.00	£20,750.00
	Jacketed tank 2 300L	SS jacketed IDMC	1	£5,500	£10,100.00	£15,600.00
	Agitator 2		1	£3,000	£1,250.00	£4,250.00
	Pump 2		1	£1,000	£3,650.00	£4,650.00
	Jacketed tank 3 100L	SS jacketed IDMC	1	£4,000	£6,350.00	£10,350.00
	Agitator 3		1	£2,500	£1,250.00	£3,750.00
	Pump 3		1	£1,000	£2,150.00	£3,150.00
	Small filtration system		1	£5,000	£650.00	£5,650.00
	Tank 4 50L	Plastic drum	1	£500	£0.00	£500.00
	Agitator 4		1	£1,000	£650.00	£1,650.00
	Pump 4		1	£1,000	£650.00	£1,650.00
Drying/filling	Fluid bed drier 10kg	Wintech FBD 10kg/35L	1	£15,000	£4,850.00	£19,850.00
Total				**£101,500**	**£57,050**	**£158,550**

Attachment 6b – API Equipment Costings Option 2

AREA	EQUIPMENT NAME	POSSIBLE SUPPLIERS	NO	UNIT PRICE (India)	Ancillaries (piping, electrics etc)	TOTAL PRICE (Far East)
Dispensary	Dust Control Booth	Extract Technology	1	£10,000	£650.00	£10,650.00
	S/S Hand Pallet Truck	Syspal	1	£500	£0.00	£500.00
	Platform Balance	Mettler, Sartorius, Stevens	1	£2,000	£650.00	£2,650.00
	Bench-top Balance	Mettler, Sartorius, Stevens	1	£1,000	£0.00	£1,000.00
	Bench Stock Bins	Pharmatech Equipment, Adelphi	3	£100	£0.00	£100.00
IPC lab	Moisture test/balance		1	£2,000	£650.00	£2,650.00
	Spectrophotometer		1	£8,000	£650.00	£8,650.00
Pre-drying	Tray drier	Wintech tray drier 24 trays	1	£15,000	£2,900.00	£17,900.00
Process room	Drum lifter		1	£2,000	£0.00	£2,000.00
	Jacketed tank 1 1000L	SS jacketed IDMC	1	£11,000	£13,350.00	£24,350.00
	Agitator 1		1	£4,000	£1,250.00	£5,250.00
	Pump 1		1	£1,500	£3,650.00	£5,150.00
	Large filtration system	ChemPro 0.50m²	1	£20,000	£9,750.00	£29,750.00
	Jacketed tank 2 750L	SS jacketed IDMC	1	£9,000	£13,350.00	£22,350.00
	Agitator 2		1	£3,700	£1,250.00	£4,950.00
	Pump 2		1	£1,500	£3,650.00	£5,150.00
	Jacketed tank 3 250L	SS jacketed IDMC	1	£5,000	£10,100.00	£15,100.00
	Agitator 3		1	£3,000	£1,250.00	£4,250.00
	Pump 3		1	£1,500	£2,150.00	£3,650.00
	Small filtration system		1	£3,000	£650.00	£3,650.00
	Tank 4 125L	SS jacketed IDMC	1	£4,000	£3,750.00	£7,750.00
	Agitator 4		1	£2,500	£650.00	£3,150.00
	Pump 4		1	£1,000	£2,150.00	£3,150.00
Drying/filling	Fluid bed drier 30kg	Wintech FBD 30kg/100L	1	£20,000	£6,350.00	£26,350.00
Total				**£131,300**	**£78,800.00**	**£210,100.00**

Attachment 6c – API Equipment Costings Option 3

AREA	EQUIPMENT NAME	POSSIBLE SUPPLIERS	NO	UNIT PRICE (India)	Ancillaries (piping, electrics etc)	TOTAL PRICE (Far East)
Dispensary	Dust Control Booth	Extract Technology	1	£10,000.00	£650.00	£10,650.00
	S/S Hand Pallet Truck	Syspal	1	£500.00	£0.00	£500.00
	Platform Balance	Mettler, Sartorius, Stevens	1	£2,000.00	£650.00	£2,650.00
	Bench-top Balance	Mettler, Sartorius, Stevens	1	£1,000.00	£0.00	£1,000.00
	Bench Stock Bins	Pharmatech Equipment, Adelphi	3	£100.00	£0.00	£100.00
IPC lab	Moisture test/balance		1	£2,000.00	£650.00	£2,650.00
	Spectrophotometer		1	£8,000.00	£650.00	£8,650.00
Pre-drying	Tray drier	Wintech tray drier 48 trays	1	£20,000.00	£2,900.00	£17,900.00
Process room	Drum lifter		1	£2,000.00	£0.00	£2,000.00
	Jacketed tank 1 2000L	SS jacketed IDMC	1	£16,000.00	£13,350.00	£24,350.00
	Agitator 1	SS jacketed IDMC	1	£5,000.00	£1,250.00	£5,250.00
	Pump 1		1	£1,800.00	£3,650.00	£5,150.00
	Large filtration system	ChemPro 1.0m²	1	£20,000.00	£9,750.00	£29,750.00
	Jacketed tank 2 1500L	SS jacketed IDMC	1	£13,500.00	£13,350.00	£22,350.00
	Agitator 2	SS jacketed IDMC	1	£4,000.00	£1,250.00	£4,950.00
	Pump 2		1	£1,800.00	£3,650.00	£5,150.00
	Jacketed tank 3 500L	SS jacketed IDMC	1	£7,500.00	£10,100.00	£15,100.00
	Agitator 3	SS jacketed IDMC	1	£3,500.00	£1,250.00	£4,250.00
	Pump 3		1	£1,500.00	£2,150.00	£3,650.00
	Small filtration system		1	£4,000.00	£650.00	£3,650.00
	Tank 4 250L	SS jacketed IDMC	1	£5,000.00	£3,750.00	£7,750.00
	Agitator 4	SS jacketed IDMC	1	£3,000.00	£650.00	£3,150.00
	Pump 4		1	£1,000.00	£2,150.00	£3,150.00
Drying/filling	Fluid bed drier 60kg	Wintech FBD 60kg/215L	1	£25,000.00	£6,350.00	£26,350.00
Total				**£158,200**	**£91,800.00**	**£250,000.00**

Attachment 7 – Quotation from Azopharma

I. Introduction

Azopharma Contract Pharmaceutical Services is committed to providing the highest quality pharmaceutical product development services available in the industry. At Azopharma, we are proud of our record of providing over forty years of high quality product development services to over 6,000 clients across the United States, Europe, and Asia. Our service offerings cover the complete spectrum of services required to develop and commercialize pharmaceutical products; discovery, preclinical, bioanalytical, synthesis, characterization, analytical, pre-formulation, formulations, CTM manufacturing, stability, Human Clinical Trials, Drug Delivery, and Regulatory affairs. Our facilities are registered with the Food and Drug Administration (FDA) and all other required regulatory governing bodies. We operate within current Good Laboratory/Manufacturing/Clinical Practices (GXP's) and have an independent Quality Assurance program for all of our operations. Quality Assurance ensures all data are 100% reviewed and every report is checked in duplicate. We employ scientists having unique combinations of education, experience, and training pursuant to guidelines dictated by the Code of Federal Regulations (CFR). Instrumentation and equipment utilized in our facilities have operational, performance, and calibration criteria and records to ensure complete data traceability. This combination of business, compliance, and training systems offers our clients a compelling solution in pharmaceutical product development.

At the request of PJB Consultancy Services (hereafter referred to as "Sponsor"), Azopharma Contract Pharmaceutical Services (hereafter referred to as "Azopharma") will perform analytical method development and minimal validation for the finished drug products. Azopharma will perform formulation activities for development of prototype formulations for support of the manufacturing of a capsule or tablet formulation(s) exhibiting a sustained drug delivery profile to include multiple dosage strength, i.e. 30mg, 60mg, and 90mg per unit dose. Azopharma will provide associated analytical support and stability protocols and studies in association with these activities.

II. Project Assumptions

The following assumptions have been made in the preparation of this proposal. If upon further review and discussion these assumptions change, prices will be adjusted accordingly.

1. **Goal:** The goal of this project is to perform analytical method development and minimal validation for the finished drug products. Azopharma will perform formulation activities for development of prototype formulations for support of the manufacturing of a capsule or tablet formulation(s) exhibiting a sustained drug delivery profile to include multiple dosage strength, i.e. 30mg, 60mg, and 90mg per unit dose. Azopharma will provide associated analytical support and stability protocols and studies in association with these activities.
2. **Intellectual Property:** Sponsor is responsible for performing intellectual property searches for composition and method of use patents for the formulations developed by Azopharma for sustained release formulations of Morphine Sulfate to ensure patentability and/or patent infringement is suitably protected or allowable.
3. **Quality Standards:** All development activities will be conducted as non-GXP, but under Azopharma's Standard Operating Procedures and Sponsor approved protocols and methods. All analytical work will be performed in accordance with Azopharma's Standard Operating Procedures, Sponsor approved protocols and methods, and cGXP regulatory guidelines, where applicable.

4. **Project Management:** Azopharma will provide project management support to monitor the progress of the project against established timelines and provide updates to the Sponsor regarding any changes that impact the predefined project timelines. Azopharma's project manager will be an extension of the Sponsor's Project Team and act as the leader of Azopharma's Pharmaceutical Development Subteam.
5. **Reference Materials:** Azopharma will source the required reference materials to include active pharmaceutical ingredient and related substances in support of the analytical testing performed at Azopharma. Azopharma will invoice the cost of materials back to Sponsor as pass-through costs.
6. **API Supply and Technical Package:** Azopharma will source sufficient amounts of the specified API along with technical package containing the analytical methods, specifications and process impurities/related compounds as related to the API, if available. Azopharma will invoice the cost of materials back to Sponsor as pass-through costs.
7. **Supply of Excipients and Packaging Components:** Azopharma will source excipients, packaging and labeling supplies in support of manufacturing. Cost of excipients, packaging, and labeling supplies will be charged back to sponsor as a pass-through cost.
8. **Sponsor Document Review:** In consultation with the Sponsor, Azopharma will prepare and submit all protocols, specifications and batch records before they are used in analysis or manufacturing for Sponsor review and approval.
9. **Official Specifications:** Azopharma will establish and provide official specifications for the API, excipients, packaging, labeling materials, and the finished product based on supplied information and FDA guidance. The specifications will be submitted to Sponsor for assessment and approval.
10. **API Raw Material Release Testing:** Azopharma will perform release analysis of the API according to the Sponsor-approved specifications. It is anticipated Azopharma will accept the API on Certificate of Analysis and perform an identification test. Upon Sponsor's request, Azopharma will perform API release analysis according to the USP/NF Monograph for Morphine Sulfate and may include: appearance, identifications (A, B, C, D), Specific Rotation <781S>, Acidity, water method I <921>, Residue on Ignition <281>, Chloride, Ammonium Salts, Limit of Foreign Alkaloids, Organic Volatile Impurities, Method I <467> and assay.
11. **Analytical Method Development and Minimal Validation for the Finished Drug Products:** Azopharma will develop and validate a method for the capsule or tablet finished drug products for Assay and Chromatographic Purity. The method will be validated to the appropriate level for in accordance with FDA and ICH regulatory guidelines. The assay and chromatographic purity method from the USP/NF Monographs for Morphine Sulfate and Morphine Sulfate Extended Release Capsules will be used as a starting point for development of the method for the finished drug products. Minimal validation activities may include sample preparation, system suitability, linearity (5-point), precision (repeatability), accuracy, and, specificity.
12. **Analytical Method Development and Minimal Validation for Dissolution for the Finished Drug Products:** Azopharma will develop and validate a method for the capsule finished drug product formulation for dissolution to measure the sustained drug delivery release rate of the API. The method will be validated to the appropriate level in accordance with FDA and ICH regulatory guidelines. The assay and chromatographic purity method from the USP/NF Monographs for Morphine Sulfate and Morphine Sulfate Extended Release Capsules will be used as a starting point for development of the method for the finished drug products. Minimal validation activities may include sample

preparation, system suitability, linearity (5-point), precision (repeatability), accuracy, and specificity.

13. **Analytical Method Development and Validation for Cleaning Verification:** Azopharma will develop and validate cleaning methods for the processing room and production equipment. Method development will use the developed assay and chromatographic purity analytical method as a starting point. The method will be validated to the appropriate level in accordance with FDA and ICH regulatory guidelines. Minimal validation activities may include sample preparation, system suitability, linearity (5-point), precision (repeatability), accuracy, and specificity.
14. **Pre-formulation Activities for Capsule Formulation:** Azopharma will perform necessary pre-formulation studies in support of formulation and process development activities. These studies may include: particle size distribution analysis, bulk/tap density, flowability, compressibility (for tablet), API-Excipient interaction, Excipient-Excipient interaction, and solubility.
15. **Formulation Development and Prototype Development Batches for Capsules:** Azopharma will manufacture up to three (3) prototype batches of the capsule or tablet sustained release formulation finished drug products for each dosage strength (30mg, 60mg, and 90mg). It is anticipated each drug strength will require a specifically designed formulation which may utilize the same excipients in varying concentration or require entirely unique formulation development to maintain similar unit sizes. The manufacturing processes for the capsule or tablet formulations may incorporate the following steps: 1.0 to 2.0 kg batch sizes, Blending, sieving, granulation, micronization (if necessary), roller compaction, tablet compression, encapsulating, and packaging. The manufactured batches will be packaged appropriately and placed under ICH storage conditions for a short-term feasibility stability study.
16. **Reporting:** Azopharma will prepare a detailed technical report to include method development and validation activities, prototype and stability activities, Batch Records, as well as a detailed summary of the release and stability results for the Sponsor's formulations in standard Azopharma format for Sponsor's assessment.
17. Azopharma will generate all relevant protocols related to activities described in this proposal for Sponsor's approval.
18. Project supplies such as, but not limited to, standards, excipients, shipping, columns and/or specialty chemicals and supplies required for execution of activities outlined in this proposal will be purchased by Azopharma and billed to Sponsor as pass-through costs once the order has been placed.
19. Work performed will be done as outlined in this proposal and in accordance with Azopharma's Standard Operating Procedures, Sponsor-approved protocols/documents, and cGXP regulatory guidelines, where applicable.
20. A 5.0% waste disposal fee will be added upon issuance of invoice.
21. The TERMS and CONDITIONS of this proposal are included as attachments. Signature of proposal by Sponsor binds Sponsor to stated terms and conditions.
22. A Sample Submission Form is attached for Sponsor's reference and use.

III. Deliverables/Costs

The deliverables and costs associated with this study are summarized in Table 1.

Table 1: Tablet or Capsule Development for Morphine Sulfate Sustained Release Formulations

Study Description	Cost[1]
Goal: The goal of this project is to perform analytical method development and minimal validation for the finished drug products. Azopharma will perform formulation activities for development of prototype formulations for support of the manufacturing of a capsule or tablet formulation(s) exhibiting a sustained drug delivery profile to include multiple dosage strength, i.e. 30mg, 60mg, and 90mg per unit dose. Azopharma will provide associated analytical support and stability protocols and studies in association with these activities.	
Intellectual Property: Sponsor is responsible for performing intellectual property searches for composition and method of use patents for the formulations developed by Azopharma for sustained release formulations of Morphine Sulfate to ensure patentability and/or patent infringement is suitably protected and/or allowable.	**Sponsor**
Quality Standards: All development activities will be conducted as non-GXP, but under Azopharma's Standard Operating Procedures and Sponsor approved protocols and methods. All analytical work will be performed in accordance with Azopharma's Standard Operating Procedures, Sponsor approved protocols and methods, and cGXP regulatory guidelines, where applicable.	**Included**
Task 1.1: Project Management: Azopharma will provide project management support to monitor the progress of the project against established timelines and provide updates to the Sponsor regarding any changes that impact the predefined project timelines. Azopharma's project manager will be an extension of the Sponsor's Project Team and act as the leader of Azopharma's Pharmaceutical Development Subteam.	**Included**
Task 1.2: Reference Materials: Azopharma will source the required reference materials to include active pharmaceutical ingredient and related substances in support of the analytical testing performed at Azopharma. Azopharma will invoice the cost of materials back to Sponsor as pass-through costs.	**Sponsor** **Or** **Pass-Through Costs**
Task 1.3: API Supply and Technical Package: Azopharma will source sufficient amounts of the specified API along with technical package containing the analytical methods, specifications and process impurities/related compounds as related to the API, if available. Azopharma will invoice the cost of materials back to Sponsor as pass-through costs.	**Sponsor**
Task 1.4: Supply of Excipients and Packaging Components: Azopharma will source excipients, packaging and labeling supplies in support of manufacturing. Cost of excipients, packaging, and labeling supplies will be charged back to sponsor as a pass-through cost.	**Pass-Through Costs**
Task 1.5: Sponsor Document Review: In consultation with the Sponsor, Azopharma will prepare and submit all protocols, specifications and batch records before they are used in analysis or manufacturing for Sponsor review and approval.	**Included**

Table 1: Tablet or Capsule Development for Morphine Sulfate Sustained Release Formulations

Study Description	Cost[1]
Task 1.6: Official Specifications: Azopharma will establish and provide official specifications for the API, excipients, packaging, labeling materials, and the finished product based on supplied information and FDA guidance. The specifications will be submitted to Sponsor for assessment and approval.	**$4,500**
Task 1.7: API Raw Material Release Testing: Azopharma will perform release analysis of the API according to the Sponsor-approved specifications. It is anticipated Azopharma will accept the API on Certificate of Analysis and perform an identification test. Upon Sponsor's request, Azopharma will perform API release analysis according to the USP/NF Monograph for Morphine Sulfate and may include: appearance, identifications (A, B, C, D), Specific Rotation <781S>, Acidity, water method I <921>, Residue on Ignition <281>, Chloride, Ammonium Salts, Limit of Foreign Alkaloids, Organic Volatile Impurities, Method I <467> and assay.	*$575 (CofA and ID)* *$5,650 per Lot (Optional: full release)*
Task 1.8: Analytical Method Development and Minimal Validation for the Finished Drug Products: Azopharma will develop and validate a method for the capsule or tablet finished drug products for Assay and Chromatographic Purity. The method will be validated to the appropriate level for in accordance with FDA and ICH regulatory guidelines. The assay and chromatographic purity method from the USP/NF Monographs for Morphine Sulfate and Morphine Sulfate Extended Release Capsules will be used as a starting point for development of the method for the finished drug products. Minimal validation activities may include sample preparation, system suitability, linearity (5-point), precision (repeatability), accuracy, and, specificity.	**Development: $20,000 per method** **Minimal Validation: $15,000 per method**
Task 1.9: Analytical Method Development and Minimal Validation for Dissolution for the Finished Drug Products: Azopharma will develop and validate a method for the capsule finished drug product formulation for dissolution to measure the sustained drug delivery release rate of the API. The method will be validated to the appropriate level in accordance with FDA and ICH regulatory guidelines. The assay and chromatographic purity method from the USP/NF Monographs for Morphine Sulfate and Morphine Sulfate Extended Release Capsules will be used as a starting point for development of the method for the finished drug products. Minimal validation activities may include sample preparation, system suitability, linearity (5-point), precision (repeatability), accuracy, and specificity.	**Development: $20,000 per method** **Minimal Validation: $15,000 per method**
Task 1.10: Analytical Method Development and Validation for Cleaning Verification: Azopharma will develop and validate cleaning methods for the processing room and production equipment. Method development will use the developed assay and chromatographic purity analytical method as a starting point. The method will be validated to the appropriate level in accordance with FDA and ICH regulatory guidelines. Minimal validation activities may include sample preparation, system suitability, linearity (5-point), precision (repeatability), accuracy, and	**$22,500**

Table 1: Tablet or Capsule Development for Morphine Sulfate Sustained Release Formulations

Study Description	Cost[1]
specificity.	
Task 1.11: Pre-formulation Activities for Capsule Formulation: Azopharma will perform necessary pre-formulation studies in support of formulation and process development activities. These studies may include: particle size distribution analysis, bulk/tap density, flowability, compressibility (for tablet), API-Excipient interaction, Excipient-Excipient interaction, and solubility.	**Estimated at 100-160 hours $17,500 – $28,000**
Task 1.12: Formulation Development and Prototype Development Batches for Capsules: Azopharma will manufacture up to three (3) prototype batches of the capsule or tablet sustained release formulation finished drug products for each dosage strength (30mg, 60mg, and 90mg). It is anticipated each drug strength will require a specifically designed formulation which may utilize the same excipients in varying concentration or require entirely unique formulation development to maintain similar unit sizes. The manufacturing processes for the capsule or tablet formulations may incorporate the following steps: 1.0 to 2.0 kg batch sizes, Blending, sieving, granulation, micronization (if necessary), roller compaction, tablet compression, encapsulating, and packaging. The manufactured batches will be packaged appropriately and placed under ICH storage conditions for a short-term feasibility stability study.	**$12,500 per Prototype Up to (9) Total**
Task 1.13: Reporting: Azopharma will prepare a detailed technical report to include method development and validation activities, prototype and stability activities, Batch Records, as well as a detailed summary of the release and stability results for the Sponsor's formulations in standard Azopharma format for Sponsor's assessment.	**Included**
Estimated Total Costs	**$237,500**

Italicized pricing is not included in the estimated total costs for each Milestone.

[1] **Note that any work performed outside the scope of services (i.e., OOS investigations, additional requests from Sponsor, product failures, etc) will be billed at a rate of $175 per hour. Up to 40-hours may be billed for such activities associated with this proposal. If Azopharma error is determined to be responsible for the additional work, no additional charges will be billed.**

IV. Payment Schedule

Sponsor will be invoiced 30% upon Sponsor's signature of Proposal, 40% at mid-point of project, 20% at completion of project work, and the 10% balance upon issuance of study report, on a per milestone basis as described within this proposal.

Should Sponsor cancel any part of this project after initiation, Sponsor may be assessed a Cancellation Fee of 20% of the total cost of the quotation and will reimburse Azopharma for any costs incurred directly related to the project. Sponsor shall pay Azopharma, on a pro-rated basis for any services rendered to the date of termination.

Azopharma reserves the right not to initiate any work until owed monies are received.

A Waste Disposal Fee (5% of invoice) will be added at time of billing and is not included in the cost tables.

Please return one (1) signed copy of this quotation to: approvals@azopharma.com (for digital copies, preferred)

Or fax to (954) 272-7030

Hard Copies may be sent to:
Azopharma Contract Pharmaceutical Services
Attention: Approvals c/o Yanin Mesa
10320 USA Today Way
Miramar, FL 33025

Project will not initiated until a letter of intent, purchase order number or a signed copy of this quotation has been received by Azopharma.

If a purchase order (P.O.) number is required for payment to Azopharma, please add the applicable P.O. number in the space provided.

Signature below or issuance of a P.O. number constitutes acceptance of this quotation and the attached Terms and Conditions. This quotation will serve as our binding contract.

Rod L. Hartwig

Digitally signed by Rod L. Hartwig
DN: cn=Rod L. Hartwig, o=Azopharma Contract Pharmaceutical Services, ou=Technical Affairs, email=rhartwig@azopharma.com, c=US
Date: 2007.09.05 12:39:53 -04'00'

Prepared by: _____

Rod L. Hartwig Date
Manager, Technical Affairs
Azopharma Contract Pharmaceutical Services

Accepted by: _____

(Authorized Signature) Date
PJB Consultancy Services

If Applicable, P.O. Number: _____

Azopharma
Contract Pharmaceutical Services

SAMPLE SUBMISSION FORM
D-009 No.1 Rev. 2

REPORT TO: _____
COMPANY: _____
ADDRESS: _____
_____
PHONE: _____
FAX: _____
EMAIL: _____
BILLING ADDRESS (IF DIFFERENT):
_____
_____
_____

P.O. NO.: _____ QUOTE NO.: _____
STORAGE CONDITIONS REQUIRED:
15° TO 30°C: ☐ 2° TO 8°C: ☐ -10° TO -25°C: ☐

OTHER: _____
PLEASE INITIAL IF SPECIAL HANDELING IS REQUIRED
NOTE: MUST HAVE PRIOR LAB APPROVAL
2 – 3 DAYS (+100% Fee): ☐ 4 – 7 DAYS (+75% Fee): ☐
24-HOUR/SATURDAY/HOLIDAY SERVICE (PLEASE CALL)
IF SAMPLE IS A CONTROLLED SUBSTANCE, PLEASE INDICATE CLASS: I ☐ II ☐ III ☐ IV ☐

DEA REGISTRATION NO.: _____

Please use one line per sample; use additional forms as necessary. An MSDS is required for each sample type submitted.

Sample Description	Lot Number (and any additional information required in the analysis report	Analysis Requested/Specifications	# of Samples	AZP USE ONLY Id No.

TESTING AUTHORIZED BY (PLEASE SIGN): _____ **DATE:** _____

AZP USE ONLY

RECEIVED BY: **CLIENT NO.:** **CONDITION: GOOD ☐ DAMAGED ☐**

10320 USA Today Way · Miramar, Florida 33025 · Tel: 954.433.7480 · Fax: 954.432-9015 · www.azopharma.com