1. P DRUG PRODUCT (Paracetamol/ UNI-PHARMA Sol. iv. inf.

1g/6.7ml AMP.)

1. ***P.1 DESCRIPTION AND COMPOSITION OF THE DRUG***

***PRODUCT***

1. ***P.1.1 Description of the Drug Product***

Ampoules of clear, amber coloured glass, of 6.7 ml nominal volume, containing clear, colorless to slightly yellow (not more intensely colored than Ref. Sol. Y5, Eur. Ph. 2.2.2), odorless solution, free of visible particles. The ampoules are manufactured of borosilicate glass tubing of 1st hydrolytic class, which corresponds to the requirements of both the current Eur. Pharm. and current USP for type I pharmaceutical glass.

The ampoules are placed in a blister inner package which consists of a thermoformed PVC/ aluminium.

The blister along with a patient information leaflet is further packaged in a cardboard folding box.

***2.3. P.1.2 Composition of The Drug Product***

|  |  |
| --- | --- |
| **Quantity Where the Composition Refers to:** | **1.0** |
| **Unit of measurement:** | **mL** |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **No** | **Name of ingredient(s)** | **Reference to standards** | **Quantity** | **Unit** | **Function** |
| **Active ingredient(s):** | | | | | |
| 1. | Paracetamol | Current  Eur. Ph. | 150.000 | mg | Active substance |
| **Other ingredient(s):** | | | | | |
| 1. | Ethanol | Current  Eur. Ph. | 0.100 | ml | Solvent |
| 2. | Disodium Edetate | Current  Eur. Ph. | 0.100 | mg | Chelating agent |
| 3. | Disodium Hydrogen Phosphate Dodecahydrate | Current  Eur. Ph. | 0.750 | mg | Adjustment of pH |
| 4. | Sodium Metabisulfite | Current  Eur. Ph. | 1.000 | mg | Antioxidant agent |
| 5. | Glycerol Formal | Current  Eur. Ph. | 0.490 | ml | Solubilising agent |
| 6. | Water for Injection | Current  Eur. Ph. | q.s. 1.000 | ml | Solvent |
| 7. | Disodium Hydrogen Phosphate Dodecahydrate 1.0 M solution | Current  Eur. Ph. | q.s. pH  5.0-6.5 | ml | Adjustment of pH |

***DETAILS OF ANY OVERAGES:***

- Active substance(s): Not Applicable

- Excipient(s): Not Applicable

1. ***P.2 PHARMACEUTICAL DEVELOPMENT***

The pharmaceutical product **Paracetamol/Uni-Pharma *Sol. iv. inf. 1g/6.7 ml Amp*.** contains paracetamol as an analgesic and antipyretic agent in a concentrated solution for IV infusion.

Stability studies of the selected, optimized formula, at physical and accelerated conditions have been performed in order to validate that it remains stable throughout the shelf life of the product.

After production of trial batches and performance of the required controls, the formula described in **§ 3.2.P.1.2** was chosen as optimal.

1. ***P.2.1*. *Components of the Drug Product***

The product **Paracetamol/Uni-Pharma *Sol. iv. inf. 1g/6.7 ml Amp*.** consists of the active pharmaceutical ingredient paracetamol and excipients that are described in detail below.

1. ***P.2.1.1. Drug Substance***

*Active substance:* **PARACETAMOL**

*(Analytical Profile of Drug Substances, Volume3, Acetaminophen)*

Paracetamol is part of the class of drugs known as “aniline analgesics”. It is the active metabolite of phenacetin, once popular as an analgesic and antipyretic in its own right, but unlike phenacetin and its combinations, paracetamol is not considered to be carcinogenic at therapeutic doses. The words *acetaminophen* and *paracetamol* (both come from chemical names for the compound: *para*-acetylaminophenol and *para*­acetylaminophenol. In some contexts, it is simply abbreviated as APAP, for *N*-acetyl- para-aminophenol.

1. ***P.2.1.1.1. Appearance Color, Odor, Taste*** White, odorless, crystalline powder, possessing a bitter taste.
2. ***P.2.1.1.2. Physical Properties***

Solubility in Aqueous Solvents

Solubility of paracetamol in distilled water: 200 C, about 14.5 mg/ml

In pH buffer solution at 37 0C its solubility has been recorded as 23.8 mg/ml

**Solubility in Water Miscible Solvents**

|  |  |
| --- | --- |
| **Solvent** | **Solubility (200 C)** |
| **Ethanol (95)** | 1 in 7 |
| **Propylene Glycol** | 1 in 10 |
| **Glycerol** | 1 in 40 |

Ionisation and pH

Paracetamol is a weak acid, its saturated aqueous solution having a pH of 5.3 to 6.5 at 250 C. pKa values for paracetamol have been quoted as 10.15.

1. ***P.2.1.1.3. Synthetic Routes***

Paracetamol is synthesized by acetylation of p-aminophenol with acetic anhydrite.

1. ***P.2.1.1.4. Purification***

Crude paracetamol is purified by recrystallization from hot water. Coloured impurities are removed during the recrystalyzation by treatment or by extraction of the aqueous p- aminophenol with an organic solvent.

**Impurity Profile**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Substance** | **Origin** |  |
| **1** | **p-Nitrophenol** | Synthetic precursor |  |
| **2** | **p-Aminophenol** | Synthetic intermediate |  |
| **3** | **p-Chloroacetanilide** | Impurity |  |
| **4** | **O-Acetyl paracetamol**  **(DAPAP)** | Impurity from over acetylation of paracetamol |  |
| **5** | **Quinone Quinomine**  **meri-Quinon-imine** | Oxidation of p-Aminophenol | Give a bluish or greyish color to paracetamol |

Impurities 1, 2, 3 are controlled in raw material according to current Eur. Ph. for Paracetamol (p.2667) which sets limits only for the above mentioned impurities and for the total impurities as well.

Current Eur. Ph. for Paracetamol does not set any limit for DAPAD and Quinone in specific; the reported limit is set for “any other impurities”.

1. ***P.2.1.1.5. Stability***

**Stability to Light (Photostability)**

Paracetamol is slightly sensitive to light when in the form of a solution and may degrade by a mechanism involving pre-dissociation of the N-C bond.

Nevertheless, it was anticipated that by using type I amber glass ampoules as primary packaging material for the product, it would be protected from degradation due to light exposure.

This hypothesis was validated by means of a photostability test carried out according to specifications described in the Note for Guidance on the Photostability Testing of New Active Substances and Medicinal Products (CPMP/ ICH/ 279/95), which demonstrated that no degradation of paracetamol occurred as no impurities could be detected.

Therefore, it was deemed unnecessary to carry out any further testing, as per step 2 of the Decision Flowchart for Photostability Testing of Medicinal Products of the above­mentioned Note for Guidance.

Stability of solid paracetamol to Heat

Dry, pure, paracetamol is very stable at temperatures up to at least 45 0C. Should it however, be contaminated with traces of p-Aminophenol or be exposed to humid conditions such that hydrolysis to p-Aminophenol takes place, then further oxidative degradation of p-Aminophenol occurs characterised by a gradual color change through pink to brown and eventually to dark brown. This involves the breakdown of the p- Aminophenol to quinomimine and related compounds.

Stability of paracetamol Solutions

The degradation of paracetamol in aqueous solutions appears to be both an acid catalysed and a base catalysed reaction. It is first order with respect to the concentration of paracetamol and first order with respect to the hydrogen and hydroxyl ion concentration (Koshy K.T. and Lanh J.L., J. Pharm.Sci. 50, 113-118 - 1961).

Stability to Oxidation

Paracetamol is relatively stable to aerial oxidation unlike its hydrolysis product p- Aminophenol. Paracetamol has been used as an antioxidant for carotene in mineral oil solution.

1. ***P.2.1.2. Excipients***

To the development of this formulation specific excipients have been used which have been chosen concerning factors as the ones that follow:

* Compatibility with the active substance
* Adjustment to the conditions and the manufacturing procedure of the specific pharmaceutical form
* Chemical Inertia
* Special characteristics concerning each excipient, which contribute to the final product properties

These are summarized as follows:

Excipients described in a Pharmacopoeia:

**Disodium edetate (D-EDTA):** A chelating agent which is added as a sequestering scavenger of metal impurities that might derive from any of the constituents of the formula.

**Sodium Metabisulfite** is added as an antioxidant at concentrations of 0.01-1.0% w/v (*Handbook of Pharmaceutical Excipients, Fifth Edition, 690-692*). The sodium metabisulfite concentration decreases over time and with exposure to temperature. This decrease is anticipated, as sodium metabisulfite is consumed by being engaged in oxidative chemical reactions, thus protecting the active pharmaceutical ingredient from oxidation. The pH is also anticipated to decrease over time and with exposure to temperature as a result of the sodium metabisulfite reactivity. Appearance of the product remains unchanged.

**Ethanol (10% V/V)**, in which the paracetamol is soluble, is one of the solvents.

**Disodium phosphate dodecahydrate** is used for the adjustment of the pH of the formulation.

**Nitrogen** used for inerting the finished medicinal product which is particularly sensitive to degradation by oxygen (current Ph. Eur.).

**Water for Injection (30% V/V)**, in which the excipients Disodium edetate and Sodium metabisulfite are soluble.

**Glycerol formal**, is used in the manufacture of the paracetamol solution for injection described hereto and is a well-known excipient. Glycerol formal is considered as a substance of low toxicity and rapidly excreted via the kidneys, therefore there is no need to establish an MRL level (EMEA/MRL/108/96-FINAL). Full non-clinical assessment, featuring a toxicological protocol for animal testing, of a Finished Dosage Formulation containing Glycerol Formal may be found in Module 4 of the Product APOTEL PLUS ® INJ. SOL. (600+20)mg/4ml AMP. which is marketed in Greece since 2002.

Please refer to Section 3.3.

Each batch may contain residual amounts of formaldehyde <200 ppm, from the manufacturing process.

Glycerol formal (60% V/V) was chosen for its solubilizing properties as a solvent for a wide variety of organic chemical substances and its ability to mix with water and ethanol.

The latter solvent was also chosen for its low toxicity and physical and chemical properties perfectly suited to the preparation of solutions destined for parenteral administration.

Another reason for this choice is that this clear and colorless liquid with a low viscosity index, in addition to being capable of mixing with water and ethanol, is also chemically remarkably stable.

All of the above excipients are described in Eur. Phar. monographs and they are of the appropriate compendial quality.

The excipients are tested for microbial bioburden in compliance with the Ph. Eur. method.

All of the used excipients are common and inert, they lack toxicity and are well known in the art, since they are widely used in pharmaceutical preparations.

1. ***P.2.2. Drug Product***

**Paracetamol/Uni-Pharma *Sol. iv. inf. 1g/6.7 ml Amp*.**

The product is presented as an injectable formulation concentrate -150 mg/ml paracetamol- packaged in 6.7 ml, Type I amber glass ampoules.

1. ***P.2.2.1. Formulation Development***

As paracetamol is poorly soluble in water, co-solvents such as ethanol were added and glycerol formal was selected as a potential solubilizer for the active substance.

During stability studies no incompatibilities were found between the drug and the excipients, all of which are well-established pharmaceutical preparation ingredients.

All excipients are widely used materials in pharmaceutical formulation, with a long story of safe utilization.

The selection of all proposed excipients was properly justified during formulation development and stability studies confirmed their good compatibility with paracetamol. Formulation pH - The formulation pH is controlled using a buffering system, which was optimized during formulation development.

During stability studies at 40°C for three months the preliminary solution for injection containing 150 mg/ml paracetamol discoloured to a pink appearance, due to oxidation, whilst there was no significant deterioration of the active substance. Nevertheless, sodium metabisulfite addition to the formula, to act as an antioxidant, was deemed warranted.

No antimicrobial preservative is added to this injectable preparation as the product has adequate inherent antimicrobial activity on the grounds of the significant non-aqueous solvent loading. Moreover, the finished product is a sterile solution presented as a monodose dosage form, produced aseptically and therefore is no requirement for the inclusion of preservatives in the formulation. However, in order to enhance the antimicrobial efficacy, ethanol was added.

Stability data confirmed adequate stability of this formulation. Other relevant tests performed during development included syringeability and closure integrity tests.

*Choice of excipients:*

The selection of excipients was thoroughly described. To enhance the solubility of Paracetamol, Glycerol formal (stabilized with the EDTA) and Ethanol were used.

An antioxidant, Sodium Metabisulfite, with the chelating agent D-EDTA is also included in the formulation to reduce oxidative degradation and maintain good product appearance.

The final formulation does not include any antimicrobial preservatives, due to self­preserving properties, compliant with the Ph. Eur. 5.1.3 Efficacy of Antimicrobial Preservation.

The different parts of the dossier substantiate the development of a concentrate for solution for infusion of acceptable chemical and pharmaceutical quality.

Pre-formulation studies were carried out in order to identify the solubility and stability characteristics of Paracetamol.

As concluded by the pre-formulation and formulation screening and optimization studies, stability of the selected formula is maintained even at a pH range of 3.8-6.5. This flexibility deriving from the robustness of the formulation was utilized in order to allow the inclusion of the selected anti-oxidant- Sodium Metabisulfite- in the formula, since the anti-oxidant, through its mechanism of action (protective against the oxidation of paracetamol) contributes to a drop of the pH throughout the shelf-life of the product, within the abovementioned specified range. For a full discussion of this phenomenon please refer to section **3.2.P.2.2.3**.

A program of drug substance stress testing under extremes of heat, light, acidic/basic and oxidative conditions has been performed. P-aminophenol appears to be the only impurity. P-aminophenol is formed during shelf-life.

Manufacture of this kind of solution has to overcome the problem of the limited solubility of paracetamol in water, which is the solvent of choice for parenteral preparations.

After solubility trials, a mixture of 3 solvents was thus chosen:

- Water for injections (30% V/V), in which additives are soluble,

- Ethanol (10% V/V), in which paracetamol is soluble,

- Glycerol formal pre stabilized with EDTA (60% V/V), chosen for its solubilizing properties as a solvent for a wide variety of organic chemical substances, and its ability to mix with water and ethanol.

The following substances were added to the formula:

- Sodium metabisulfite, an antioxidant preservative added at concentration (0.1% m/V) sufficient to stabilize the preparation against any chemical breakdown of paracetamol (oxidation of p-aminophenol towards quinine imine liable to polymerization with p-aminophenol resulting to the formation of coloured derivative products);

- Disodium phosphate dodecahydrate, used to adjust the pH of the preparation between 5.0 and 6.5 at the time of batch release, in order to avoid any hydrolysis of paracetamol in the aqueous medium resulting to the formation of p-aminophenol. The pH of range of 5.0-6.5 is specified as a quality parameter for the release of the finished product.

Of course, as mentioned above, throughout the shelf life of the finished product, a pH range of 3.8-6.5 becomes applicable as a quality specification due to the phenomenon of the consumption of sodium metabisulfite, which leads to the decrease of the pH value. The above pH range is relevant as documented by stability studies of the optimal formulation.

1. ***P.2.2.2. Overages*** Not applicable.
2. ***P.2.2.3. Physicochemical and Biological Properties***

In this section the physicochemical parameters relevant to the performance of the drug product are discussed. Taking into consideration the pharmaceutical form of the medicinal product, the physicochemical property that should be addressed is the pH of the solution. A major concern was the drop in the pH of the solution due to the consumption of Sodium metabisulfite. Reducing agents such sulfite, bisulfite and metabisulfite are preferentially oxidized due to a lower redox potential than the drug or other excipients in the formulation. Sodium Metabisulfite (S2O52-) is an antioxidant that has been used in parenteral preparations for decades. In the APOTEL formulation, it is present in equilibrium and has the potential to initiate radical chain reactions. Salts of sulfite, bisulfite and metabisulfite are oxygen scavengers with a high aqueous solubility. They are the most common antioxidants in parenteral products. *(Handbook of Pharmaceutical Excipients, Fifth Edition,690-692)*.

Degradation of glycerol formal

According to the CoA of the manufacturer for Glycerol Formal, free formaldehyde is presented in the raw material.

C4H8O3 + H2O C3H8O3 + CH2O

Glycerol formal Water Glycerol Formaldehyde

In addition, formaldehyde is considered to be a degradation product of glycerol formal, as it can be noted from the figure above. 1 mol of glycerol and 1 mol of formaldehyde are produced after the degradation of 1 mol of glycerol formal.

Taking tolerability levels into account (United Nations Environmental Program, Formaldehyde Report), a limit of 100 pg/ml is considered to be acceptable. Moreover, the limit set for formaldehyde by the European Pharmacopoeia for Glycerol Formal Monograph is 200ppm.

Actually, the limit for free formaldehyde during intake by patients of the end solution, prepared by dilution of the ampoule concentrate, is 7 pg/ml, well below the accepted concentration cited under the above mentioned reference, since the ampoule content is diluted in 100ml of a 0.9% w/v NaCl solution prior to administration.

**Degradation of Metabisulfite**

**Na2S2O5 + H2O —► 2Na+ + 2HS03-**

2HSO3- + 2H2O2 —► 2SO42- + 2H+ + 2H2O

According to the suggested mechanisms presented above, the product of the consumption of the antioxidant in **Paracetamol/Uni-Pharma *Sol. iv. inf. 1g/6.7 ml Amp*.** is mainly expected to be the sulfate ion with simultaneous production of hydrogen cations *(Ref. M.R.Hoffmann and J.O. Edwards, Kinetics of the oxidation of Suflite by Hydrogen Peroxide in Acidic Solution, The journal of Physical Chemistry, Vol. 79, No 20, 1975)*. The result of this chemical reactivity is the lowering of the pH of the solution and the consumption of Sodium metabisulfite. Sulfate ions are considered as non toxic for humans and therefore it is not necessary for an upper limit to be established (Ref. **WHO/SDE/WSH/03.04/114, Sulfate in Drinking-water** Background document for development of WHO *Guidelines for Drinking-water Quality*)*.*

Therefore the specified range for Sodium metabisulfite over the shelf life of the product, as documented by the stability studies of the optimal formulation, is 10-110% and applicable as a quality parameter *(see also section* ***3.2.P.8.1.2.****)*, whereas due to the same phenomenon the pH range applicable as a quality parameter over the shelf life of the product, is specified at 3.8-6.5 *(see section* ***3.2.P.8.1.2.****)*.

Using the semi-quantitative method for sulfate ion determination {Eur. Phar. (2.4.13)}, along with method B {Eur. Phar (2.4.18)} for determination of free formaldehyde, and the method of determination of Glycerol (current Eur. Phar.) the corresponding concentrations of the sulfate ion, formaldehyde and Glycerol in different batches of the product **Paracetamol/Uni-Pharma *Sol. iv. inf. 1g/6.7 ml Amp*.** were determined. All of the above mentioned methods were adapted and validated by the Quality Control department of UNI-PHARMA S.A. The results together with the value of pH and quantification of the antioxidant are shown in the following table (Table 1).

Careful selection of supplies of glass ampoules and testing of all new lots of glass ampoules was applied prior to the manufacture of **Paracetamol/Uni-Pharma *Sol. iv. inf. 1g/6.7 ml Amp*.**, in order to avoid compatibility issues with the solution concerning physicochemical properties.

**Table 1**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **APOTEL® SOL. IV. INF. 1000mg/6.7ml AMP.** | | | | | | | | | |
| **LOT No** | **PRODUCTION DATE** | **TIME FROM**  **PRODUCTION DATE**  **(MONTHS)** | **STABILITY CONDITIONS** | **Sulfate ion**  **(ppm)** | **Glycerin Max 0.5 %** | **Free Formaldehyde**  **Max 100 (pg/ml)** | **pH** | **ASSAY**  **(METABISULFITE)**  **(%)** | |
| **T=0 months** | **T= time from production date** |
| **05­**  **01D** | 12/2005 | 36 | 25 ±  2 °C | 850 | 0.25 | <100 | 4.2 | 108 | 35 |
| **06­**  **01D** | 10/2006 | 30 | 25 ±  2 °C | 810 | 0.20 | <100 | 4.3 | 103.9 | 41 |
| **06­**  **02D** | 10/2006 | 30 | 25 ±  2 °C | 840 | 0.21 | <100 | 4.2 | 104 | 35 |
| **08­**  **01** | 02/2008 | 6 | 40 ±  2 °C | 780 | 0.15 | <100 | 4.35 | 108 | 43 |
| **08­**  **01** | 02/2008 | 18 | 30 ±  2 °C | 650 | 0.17 | <100 | 4.8 | 108 | 55 |

1. ***P.2.3. Manufacturing Process Development***

**Method of preparation**

The manufacturing process is well controlled and in-process testing is adequate to ensure consistent quality in the product.

**Control of starting materials**

***Active substance:* PARACETAMOL**

According to current Ph. Eur.

A detailed specification for the active substance including tests for appearance, particle size, identification, total viable aerobic count, combined yeast and moulds, specified microorganisms, related substances, residual solvents, loss on drying, sulfated ash, heavy metals, clarity and colour of solution and assay was provided.

The active is packaged in a double polyethylene liner (double layers of low density PE) in drums.

***Excipients:***

Glycerol formal, Ethanol anhydrous, Sodium metabisulfite, Disodium phosphate dodecahydrate, Water for Injection, D-EDTA, and Nitrogen comply with the appropriate current monographs of the Ph. Eur. or the in house methods.

The excipients are tested for microbial bioburden according to the current Ph. Eur. method.

The manufacture of the solution for injection is based essentially on the dissolution of the active substance in a cosolvent system. The dissolution is facilitated by ensuring that the pH of the solution lies in a range at which the active substance is stable. The most critical step of the process is to ensure that the manufacture is conducted in an atmosphere free of oxygen, since the active substance is prone to oxidation, when in the form of a solution.

Terminal sterilization with moist heat is not possible due to the increase in total degradation product levels it causes., A combination of aseptic filtration and aseptic processing has to be followed, instead. Final full scale batches showed full compliance with the finished product specifications.

The two following minor points of process parameter adjustments have been established:

* The holding time prior to filtration has been reduced to 4 hours.
* Over killing conditions during the production are used to provide a sterility assurance level (SAL) of 10-8.

The impact on p-aminophenol formation is minor, from 0.0% to 0.0001%.

The manufacturing formulae for the proposed batch sizes were presented for the solution for injection formulations.

The manufacturing process for the solution for injection is a standard process consisting of a solution preparation followed by sterilisation by filtration and filling into ampoules in an aseptic processing zone. The sterilisation methods of equipment and primary packaging are considered appropriate. The manufacturing process has been described in sufficient detail. Details of the in-process controls including pH measurements , clarity, bioburden level, filter integrity, fill volume/weight, oxygen headspace and vial defect controls along with the specifications set were provided.

Batch analysis data for the solution for injection demonstrate that the respective manufacturing process consistently renders a product that meets the required specifications.

Satisfactory process validation data demonstrate the processes to be reliable and robust and a validation protocol for the initial commercial batches was presented.

Control of finished product

The finished product consists of an aqueous organic solution (150 mg/ml paracetamol) adjusted to a target pH value of 6.4.

***Solution for infusion - Specifications of the finished product***

|  |  |
| --- | --- |
| ***Determinations*** | ***Specifications*** |
| ***Appearance*** | Limpid, colorless to slightly yellow, odorless solution free of visible particles |
| ***Identification of Paracetamol*** | 1. HPLC - Retention time: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation. 2. HPLC - Diode array: The spectra of the peak of the drug substance in the sample solution is identical to the spectra of the peak of the drug substance in the standard preparation. |
| ***Identification of Sodium***  ***Metabisulfite*** | Iodometric method |
| ***Assay of Paracetamol*** | 95.0-105.0% at the time of batch release and during shelf-life of the product. |
| ***Assay of Sodium Metabisulfite*** | 80.0-110.0% at the time of batch release  10.0-110.0% during shelf-life of the product |
| ***Related Substances (HPLC***  ***method)*** | p-Aminophenol : NMT 0.50 % of paracetamol content |
| ***pH value*** | 5.0-6.5 at the time of the batch release  3.8-6.5 during the shelf-life of the product |
| ***Extractable volume*** | Any individual container NLT 6.7 ml |
| ***Particulate Contamination*** |  |
| ***-Visible particles*** | Current Eur. Pharm. § 2.9.20. |
| ***-Sub-Visible particles*** | Current Eur. Pharm. § 2.9.19 Method 2 Test 2B. |
| ***Relative Density*** | 1.145 ± 5% at the time of batch release |
| ***Sterility*** | Sterile according to Ph. Eur. V |
| ***Bacterial Endotoxins*** | < 13.1 UI/ml |

NMT: Not More Than

NLT: Not Less Than Detailed specifications for both release and end-of-shelf-life testing including tests for; Appearance (visual); Identification (HPLC); Refractive index, Fill volume; pH (potentiometric); Sterility (membrane filtration method, Ph. Eur.); Particulate matter, Bacterial endotoxins (gel-clot evaluation, Ph. Eur.); Assay of sodium metabisulfite (Iodometric); Assay of paracetamol (HPLC); Degradation products of glycerol formal (Formaldehyde), Degradation products of paracetamol (p-aminophenol) (HPLC) were provided.

Total degradation product (p-aminophenol) specification is NMT 0.50%.

All control methods are fully described in the current Eur. Phar. with the exception of the analytical method for assay determination of the Active Substance, which is described in the current edition of the USP. Relevant test methods have been validated according to ICH requirements. The method used for the assay of sodium metabisulfite has been sufficiently validated with respect to specificity, accuracy, repeatability and intermediate precision, linearity and range, LOQ and robustness. The HPLC method has been sufficiently validated with respect to specificity, accuracy, repeatability and intermediate precision, linearity and range, LOQ and robustness.

Forced degradation studies of the finished product in its primary packaging (with parameters such as temperature, pH, oxidation and light exposure), showed that the resulting degradation products were anticipated degradation products of the active substance. The chromatograms showed that the degradation products were well separated from the active substance and what is most important; from each other. These data provide evidence for the stability while indicating the relevance and effectiveness of the analytical method.

The test for bacterial endotoxins was sufficiently validated. The limit of detection was calculated to be 3 EU/ml which is approximately ~20% of the specified endotoxin limit (13.1 EU/ml). The other test methods are either simple or compendial methods and need no further validation.

Each batch was manufactured and released at the proposed production/release site and packaged at the proposed packaging site. Three certificates of analysis are included in the dossier. All samples passed the release criteria.

1. ***P.2.4. Container Closure System***

Based on the results of photostability study the product is considered photostable when stored in type I amber glass ampoules. Results from tests regarding container closure integrity and fragmentation/self sealability were found to be acceptable.

The primary container is a type I amber glass ampoule that protects the solution from contamination on one hand, and from light on the other, to both of which the active ingredient is sensitive. The stability trials on the final product were carried out with this type of primary packaging and showed that the solution is stable for 36 months at ambient temperature.

Satisfactory specifications for the container and closure components have been provided. The packaging materials have been subjected to rigorous integrity testing and have been found to be satisfactory.

Particular emphasis has been placed on the sourcing of glass ampoules. Particulates found in early stability studies were identified as glass, resulting from delamination of the ampoules. This has been considered critical. However, an acceptable quality level for the presence of glass particles detected by visual inspection has been provided, on the basis of a protocol for stress testing all new lots of glass ampoules prior to use in the manufacture of the product. Each batch of ampoules used is required to be qualified using satisfactory methodology.

The sterilization method of primary packaging and testing for bacterial endotoxins, complies with current ICH requirements.

The flow-chart presented below shows the packing of the injectable solution.

Flow chart - Step Nr

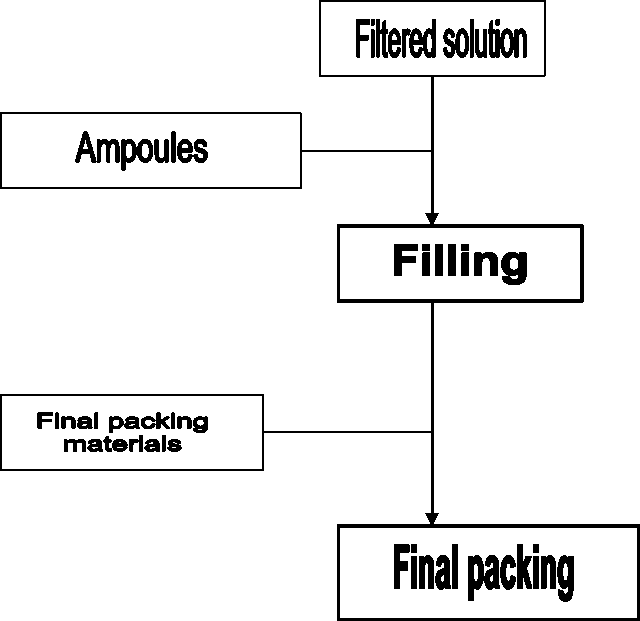
In-process controls

VI

VII

Room sterility, extractable volume, leakage tests, laminar air flow function

Conformity, counting



1. ***P.2.5. Microbiological Attributes***

The final formulation does not include any antimicrobial preservatives, due to self­preserving properties, compliant with the Ph. Eur. 5.1.3 Efficacy of Antimicrobial Preservation.

Over killing conditions during production provide a sterility assurance level (SAL) of 10-8 due to the nature of the product (Presence of ethanol-glycerol formal) (please refer to 3.2.P.3.5)

The manufacturing process for the solution is a standard process consisting of a solution preparation followed by sterilisation by filtration and filling into ampoules in an aseptic processing zone. The sterilisation methods of equipment and primary packaging comply with the current ICH requirements.

A validated aseptically based sterilisation method was adopted. *CPMP/QWP/054/98 Annex to Note for guidance on Development Pharmaceutics (CPMP/QWP/155/96): Decision Trees for Selection of Sterilisation Methods.*

1. ***P.2.6. Compatibility***

During stability studies no incompatibilities were found between the drug and the excipients, all of which are well-established pharmaceutical preparation ingredients. Compatibility studies indicated that paracetamol is stable for 4 hours in intravenous admixtures and containers **(0.9% sodium chloride**, **Lactated Ringer's,\* 3,33% Dextr./ 0,3% NaCl, 5,0% Dextr.)**.

CONCLUSIONS

The concentrate solution for infusion contains 150 mg of paracetamol per ml which can be administrated to humans after dilution to a final volume of 100 ml. It is packed in an amber glass ampoule.

Full information is provided in the dossier to justify the quality of batches. Excipients used in the manufacture of the product are considered quite common for use in injection preparations. The dossier provides a suitable description of the active substance and the chosen formulations, and confirms production of the active substance and of the final product at a consistent quality. Analytical methods are well described, and data of their validation confirm their suitability.

Manufacturing processes are sufficiently detailed for all preparations and demonstrate that production of the final product is subject to a consistent quality. The specifications for the final product contain sufficient acceptance criteria and corresponding tests. Stability studies have been performed according to ICH guidelines. The stability studies on the finished products justify a shelf-life of 3 years for the solution concentrate for infusion at a temperature below 25 oC.

1. ***P.3 MANUFACTURE***
2. ***P.3.1 Manufacture(s)***

Manufacturers of the finished dosage form:

UNI-PHARMA KLEON TSETIS PHARMACEUTICAL LABORATORIES S.A. 14th km National Road 1,

GR-145 64, Kifissia, Greece

UNI-PHARMA KLEON TSETIS, PHARMACEUTICAL LABORATORIES S.A., possesses:

* “Manufacturing Licence”
* “Good Manufacturing Practice Certificate”

from the Greek National Organization for Medicines.

1. ***P.3.2 Batch Formula***

Product:

***Paracetamol Sol. iv. inf. 1g/6.7 ml amp.***

The proposed commercial batch size of Paracetamol Sol. iv. Inf. 1g/6.7ml amp. is 200.00 L.

The qualitative and quantitative composition of the stated standard production batch of

200.00 L (or 229.00 kg since the density of the solution is considered 1.145 g/ml ± 5%) is presented in the table in section 3.2.P.3.2.

1. ***P.3.3 Manufacturing procedure***

Before the beginning of the production all the premises and equipment are properly cleaned, disinfected and sterilized.

Before the beginning of the production all the premises and equipment are properly cleaned, disinfected and sterilized.

Stage A

The production of the injectable solution is done in a Grade C clean room.

Stage A.1

Glycerol Formal and Ethanol are inserted into the stainless-steel preparation tank, and they are stirred for approximately five (5) minutes until complete mixing.

Stage A.2

Each of the following ingredients, Sodium Metabisulfite, Disodium Edetate and Disodium Hydrogen Phosphate Dodecahydrate, is dissolved one by one separately by adding 5.0 l of WFI for each into a 10.0 l vessel, which is inside the compounding room. The dissolution process is performed with the use of a magnetic stirrer. Subsequently, each solution is added to the main preparation stainless steel vessel and is stirred further for five (5) minutes.

Stage A.3

Paracetamol micronized injectable grade is inserted into the solution of the main preparation tank and is stirred further until complete dissolution, for approximately ninety (90) minutes.

Stage A.4

The pH value of the solution of stage A.3 is checked and it is adjusted using Disodium hydrogen phosphate dodecahydrate 1.0 M solution or Sodium dihydrogen phosphate dihydrate 1.0 M solution. The proper amount of Disodium hydrogen phosphate dodecahydrate or Sodium dihydrogen phosphate dihydrate is dissolved in WFI in order to acquire the 1.0 M solution. The acceptable pH range of the solution is 5.0-6.5, however, the pH adjustment target is 6.4-6.5.

Stage A.5

Water for injection is added into the solution of stage A.4 till the volume of the injectable solution is completed to 200.00 L and the final solution is stirred until complete mixing for approximately twenty (20) minutes.

Stage B

The final bulk solution is transferred to the sterile stainless steel storage tank by passing through a filtration configuration equipped with two filters, a pre-filter, Sartorius

Sartopure GF2 with pore size of 1.2pm and a sterilizing filter, Sartorius Sartobran P with pore size 0.45+0.2pm. The sterilizing filter is subjected to filter integrity test before and after the filtration.

Stage C

The empty ampoules are sterilized using the dry depyrogenation oven, at 180oC for 180 minutes. The sterility and depyrogenation of the empty ampoules have been validated. The aseptic filling of the ampoules is performed by an automated ampoules filling machine within a class A room under laminar air flow with a class B background. The volume of the content of the filled ampoules is checked periodically during the whole filling procedure. The filling volume per container is 6.9 ml in order to have extractable volume NLT 6.7 ml. Prior to sealing the ampoule headspace is filled with nitrogen gas.

Stage D

The filled ampoules are 100% optically inspected for particles larger than 20pm using an automatic machine, which also performs a check for the volume of the content of the filled ampoules and the integrity of the container.

The reliability of the aseptic manufacturing process is checked twice a year by process simulating (media fill) test.

Stage E

The ampoules are then packed in PVC/Aluminium blisters, which are further packed along with a patient information leaflet in a cardboard box.

1. ***P.3.4 Process Validation and/or Evaluation***

Validation strategy

For validation purposes twenty-one (21) commercial batches of the product

**Paracetamol *Sol. iv. inf. 1g/6.7ml AMP.*** are used, namely:

|  |  |  |  |
| --- | --- | --- | --- |
| • | **09-01** | **09-41** | **09-74** |
| • | **09-02** | **09-42** | **09-75** |
| • | **09-03** | **09-43** | **09-76** |
| • | **09-04** | **09-44** | **09-77** |
| • | **09-05** | **09-45** | **09-78** |
| • | **09-06** | **09-46** | **09-79** |
| • | **09-07** | **09-47** | **09-80** |

These batches were produced as follows:

**Table 3.2.P.3.5.1.A: Batches identity**

|  |  |  |  |
| --- | --- | --- | --- |
| **Content** | **Batch number** | **Manufacturing date** | **Batch size** |
|  | 09-01 | 05-2009 | 200.000 L |
| 150 mg/ml | to | to | 200.000 L |
|  | 09-80 | 02-2010 | 200.000 L |

All batches were manufactured following the same manufacturing process.

Please refer to Module 3 for the validation of manufacturing procedure.

1. ***P.4 CONTROL OF EXCIPIENTS***

All excipients contained in the Drug Product have a Pharmacopoeial status and specifications have been worked out in line with current Ph. Eur. Monographs.

**EXCIPIENTS DESCRIBED IN A PHARMACOPOEIA:**

|  |  |  |
| --- | --- | --- |
| **No** | **Name of ingredient** | **Reference to standards** |
| 1. | Ethanol 96.0% | Current Eur.Pharmacopoeia monograph 1317 |
| 2. | Disodium Edetate | Current Eur.Pharmacopoeia monograph 0232 |
| 3. | Disodium Hydrogen Phosphate Dodecahydrate | Current Eur.Pharmacopoeia monograph 0118 |
| 4. | Sodium Metabisulfite | Current Eur.Pharmacopoeia monograph 0849 |
| 5. | Glycerol Formal | Current Eur.Pharmacopoeia monograph 1671 |
| 6. | Water for injection | Current Eur.Pharmacopoeia monograph 0169 |
| 7. | Disodium Hydrogen Phosphate Dodecahydrate 1.0 M solution | Current Eur.Pharmacopoeia monograph 0118 |

All suppliers of the excipients are interchangeable as long as the excipients meet the finished product manufacturer's specifications. The Certificates of Analysis of some indicative suppliers can be found in the following pages.

All tests are routinely performed on receipt of excipient at the site of product manufacture.

1. ***P.5 CONTROL OF DRUG PRODUCT***
2. ***P.5.1 Specification(s)***

|  |  |
| --- | --- |
| ***Tests*** | ***Specifications*** |
| ***Appearance*** | Clear, colorless to slightly yellow, odorless solution free of visible particles |
| ***Identification of Paracetamol*** | 1. HPLC - Retention time: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation. 2. HPLC - Diode array: The spectra of the peak of the drug substance in the sample solution are identical to the spectra of the peak of the drug substance in the standard preparation. |
| ***Identification of Sodium***  ***Metabisulfite*** | Iodometric method |
| ***Assay of Paracetamol*** | 95.0%-105.0% at the time of batch release and during shelf-life of the product. |
| ***Assay of Sodium Metabisulfite*** | 80.0%-110.0% at the time of batch release  10.0%-110.0% during shelf-life of the product |
| ***Related Substances (HPLC method)*** | p-Aminophenol : NMT 0.50 % of paracetamol content |
| ***pH value*** | 5.0-6.5 at the time of the batch release  3.8-6.5 during the shelf-life of the product |
| ***Extractable volume*** | Any individual container NLT 6.7 ml |
| ***Particulate Contamination*** |  |
| ***-Visible particles*** | Current Eur. Pharm. § 2.9.20. |
| ***-Sub-Visible particles*** | Current Eur. Pharm. § 2.9.19 Method 1 Test 1B. |
| ***Relative Density*** | 1.145 ± 5% at the time of batch release |
| ***Sterility*** | Sterile according to Current Eur.Pharm. |
| ***Bacterial Endotoxins*** | < 13.1 IU/ml |

NLT: Not Less Than

NMT: Not More Than

***Proposed shelf-life***

36 months at 25OC± 2OC/ 60% RH ± 5%

36 months at 30OC± 2OC/ 65% RH ± 5%

1. ***P.5.2 Batch analyses***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ***BATCH*** | ***Manufacturing***  ***Date*** | ***Manufacturing***  ***Plant*** | ***Batch Size*** | ***Purpose of Production*** |
| **05-01 D** | 12/2005 |  | 1,000 amp |  |
| **06-01 D** | 10/2006 |  | 1,000 amp |  |
| **06-02 D** | 10/2006 | UNI-PHARMA KLEON TSETIS | 1,000 amp | Stability studies and validation of manufacturing procedure |
| **08-01** | 02/2008 | PHARMACEUTICAL  LABORATORIES S.A. | 28,900 amp |
| **09-01** | 05/2009 |  | 28,900 amp |  |
| **10-01** | 02/2010 |  | 28,900 amp |  |

1. ***P.6 REFERENCE STANDARDS OR MATERIALS***

Since Paracetamol is a Pharmacopoeia product, the reference standard is available and supplied by the European Pharmacopoeia - EDQM (related substances method).

A BP reference standard of paracetamol was also used (assay of paracetamol method). 4-Aminophenol was purchased from Sigma-Aldrich.

|  |  |  |
| --- | --- | --- |
| **Reference And Working Standards Table** | | |
| **Name** | **Lot Number** | **Potency (%)** |
| Paracetamol (obtained from EDQM) | 3 | 100.0% |
| Paracetamol BPCRS (obtained from BP) | 3516 | 99.9% |
| 4-Aminophenol (R) (obtained from Sigma-Aldrich) | SZBD1060V | 99.0% |

The respective CoAs are attached in Module 3.

1. ***P.7 CONTAINER CLOSURE***
2. ***P.7.1. Container (brief description)***

The primary container close system is ampoules of amber coloured glass with 6.7 ml nominal content. The ampoules are placed in a blister inner package which consists of a thermoformed PVC/aluminium. Each cardboard folding box contains 3 ampoules and the patient information leaflet.

The ampoules are manufactured of borosilicate glass tubing of 1st hydrolytic class, which corresponds to the requirements of both the current Eur. Pharm. and current USP for type I pharmaceutical glass.

Regarding all suitability justification please refer to 3.2.P.2

1. ***P.7.2. Type of packaging material***

Cardboard folding box containing the blister and the patient information leaflet.

1. ***P.7.3. Quality specifications (routine tests)***

The ampoules are checked on a regular basis for the following qualities: - test of physical dimensions

- integrity of material

1. ***P.7.4. Development/validation studies***

The choice of materials has been quite straightforward:

The material of the container should not interfere with its contents, which makes glass the material ideally suited.

The quality used is neutral glass of the first hydrolytic class which demonstrates highest hydrolytic resistance (glass type I / current USP, current Eur. Pharm.). The glass is amber and completely transparent, allowing thus, checking for turbidity or sediments as final precaution before administration. The ampoules are sealed by fusion and automatically controlled for pinholes to exclude any leaks or secondary contamination.

*A copy of the container closure system specifications is included in Module 3.*

1. ***P.8 STABILITY***
2. ***P.8.1 Stability Summary and Conclusion***

The regular stability program of **Paracetamol/Uni-Pharma *Sol. iv. inf. 1g/6.7 ml Amp.*** started in December 2005.

***Methodology:***

Real-time studies (physical stability) / long term stability studies

*Table 2.3.P.8.1: Stability batches- long term stability studies*

|  |  |  |
| --- | --- | --- |
| **Batch number** | **Manufacturing Date** | **Batch size** |
| 05-01D | 12/2005 | 1,000 amp |
| 06-01 D | 10/2006 | 1,000 amp |
| 06-02 D | 10/2006 | 1,000 amp |
| 08-01 | 02/2008 | 28,900 amp |
| 09-01 | 05/2009 | 28,900 amp |
| 10-01 | 02/2010 | 28,900 amp |

Storage conditions:

Controlled room temperature and humidity (25°C± 2°C/ 60% RH ± 5%).

Container Closure System:

The primary container close system is ampoules of amber coloured glass with 6.7 ml nominal content. The ampoules are placed in a blister inner package which consists of a thermoformed PVC/aluminium. Each cardboard folding box contains 3 ampoules and the patient information leaflet.

Intermediate stability studies

*Table 2.3.P.8.1: Stability batches- long term stability studies*

|  |  |  |
| --- | --- | --- |
| **Batch number** | **Manufacturing Date** | **Batch size** |
| 08-01 | 02/2008 | 28,900 amp |
| 09-01 | 05/2009 | 28,900 amp |
| 10-01 | 02/2010 | 28,900 amp |

Storage conditions:

Controlled room temperature and humidity (30 °C ± 2 °C / 65% RH ± 5%).

Container Closure System:

The primary container close system is ampoules of amber coloured glass with 6.7 ml nominal content. The ampoules are placed in a blister inner package which consists of a thermoformed PVC/aluminium. Each cardboard folding box contains 3 ampoules and the patient information leaflet.

Accelerated conditions studies (stress conditions)

*Table 2.3.P.8.2: Stability batches- Accelerated stability studies*

|  |  |  |
| --- | --- | --- |
| **Batch number** | **Manufacturing Date** | **Batch size** |
| 05-01D | 12/2005 | 1,000 amp |
| 06-01 D | 10/2006 | 1,000 amp |
| 08-01 | 02/2008 | 28,900 amp |
| 09-01 | 05/2009 | 28,900 amp |
| 10-01 | 02/2010 | 28,900 amp |

Storage conditions:

Controlled room temperature and humidity (40 °C ± 2 °C / 75% RH ± 5%).

Container Closure System:

The primary container close system is ampoules of amber coloured glass with 6.7 ml nominal content. The ampoules are placed in a blister inner package which consists of a thermoformed PVC/aluminium. Each cardboard folding box contains 3 ampoules and the patient information leaflet.

1. ***P.8.2 Post-Approval Stability Protocol and Stability Commitment***

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **CONDITION** | **TESTING INTERVALS (in months)** | | | | | | |
| **3** | **6** | **9** | **12** | **18** | **24** | **36** |
| **Long-term**  **25OC± 2OC/ 60% RH ± 5%** | **X** | **X** | **X** | **X** | **X** | **X** | **X** |
| **Intermediate**  **30OC± 2OC/ 65% RH ± 5%** | **X** | **X** | **X** | **X** | **X** | **X** | **X** |
| **Accelerated**  **40OC± 2OC/ 75% RH ± 5%** | **X** | **X** |  |  |  |  |  |

1. ***P.8.3 Stability Data***

For the stability data please refer to the tables presented in section 3.2.P.8.3.

Conclusion

The up to date stability results (Long-term stability and Accelerated stability), during the shelf life of the product, show that **Paracetamol/Uni-Pharma *Sol. iv. inf. 1g/6.7 ml Amp*** fully complies with the defined specifications in all parameters considered.

Finished product stability studies have been conducted in accordance with current guidelines.

Based on the results, a shelf-life of 36 months has been set, which is satisfactory. Storage conditions are “Do not store above 25 degrees” or “Do not store above 30 degrees”.

Proposed shelf-life:

36 months at 25 °C ± 2 °C / 60% RH ± 5%

36 months at 30 °C ± 2 °C / 65% RH ± 5%

1. A APPENDICES
2. ***A.1 Facilities and Equipment***

Facility for the production of solution for infusion.

***A) Manufacturing Equipment***

* 200 lit. stainless steel vessel for the production of injectable solution.
* 2 filtration vessels.
* Sartorius filtration apparatus with filter Sartobran P and pro-filter Sartopure GF2.
* Nitrogen tank for filtration.
* Small vessel MILLIPORE for filter check.
* pH-meter.
* PONZINI distiller unit, with stainless steel vessel for the collection of water.
* DE LAMA Sterillization Unit with temperature and time recording units.
* Impermeability check apparatus.
* Lytzen Dry Sterilization Unit with temperature and time recording units.

***B) Analytical Equipment***

* HPLC Apparatus.
* UV Apparatus.
* Precision Balance.
* TOC.
* pH-meter.

1. ***A.2 Adventitious Agents Safety Evaluation***

The under registration pharmaceutical product contains in its formulation pharmaceutical raw materials [active ingredient and excipients] that do not contain or consist of Genetically Modified Organisms (GMO).

Further more all the raw materials used during the development of the product are widely used in Pharmaceutics for a long period of time with a well documented hypotoxicity.

In addition, the manufacturing process followed for the specific pharmacotechnical form does not present any environmental risk given that the installation area and the mechanical equipment used for the production are quite new and during the production process all the necessary precautions are taken in accordance to the latest Safety Regulations.

On the basis of the above mentioned considerations, it is possible to affirm that the product is not a vehicle of transmission of agents that would be pathogen for human health.

1. ***A.3 Excipients***

No new excipients, used for the first time in the composition of the product, are included.

1. R REGIONAL INFORMATION

Not applicable.