Health Canada Santé Canada

# QUALITY OVERALL SUMMARY - CHEMICAL ENTITIES MOCK-UP ("QOS-CE MOCK-UP")

*(version 2005-05-24)*

**NOTE TO READER:**

The following *Quality Overall Summary - Chemical Entities Mock-up ("QOS-CE Mock-up")* has been prepared using Health Canada's *Quality Overall Summary - Chemical Entities (NDS/ANDS) (version 2004-04-01)* template as the basis of the document. This *QOS-CE Mock-up* is intended to provide additional guidance for summarizing the information contained in *Module 3 - Quality* of a drug submission formatted according to ICH's Common Technical Document guideline. It should be read in conjunction with the relevant ICH and Health Canada guidance documents.

The text included in this document is provided for illustrative purposes of a number of possible scenarios that could be encountered when preparing and summarizing data. Attempts have been made to maintain consistency in the information, where possible. However, it is acknowledged that not all of the information is entirely consistent throughout the document (e.g., stereochemistry information described in Module S.3.1, even though the compound described in Module S.1.1 does not contain chiral centres).

It should be ensured that a *sufficient* and an *appropriate* level of detail is included when preparing the Quality Overall Summary (QOS) to allow for an efficient review of the necessary data. The data should be summarized in an accurate, consistent, and concise manner.

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Canada

## MODULE 2.3: QUALITY OVERALL SUMMARY (QOS)

## INTRODUCTION

**(a) Summary of product information:**

| | |
|---|---|
| **Proprietary (Brand) Name of Drug Product** | AMBROSIA® Delayed-release Tablets |
| **Non-proprietary or Common Name of Drug Product** | Ambrosol Hydrochloride Delayed-release Tablets |
| **Non-proprietary or Common Name of Drug Substance (Medicinal Ingredient)** | Ambrosol Hydrochloride |
| **Company (Manufacturer/Sponsor) Name** | Drugs 'R' Us |
| **Dosage Form(s)** | Enteric-coated Tablets |
| **Strength(s)** | 25 mg, 50 mg, and 75 mg<br>(ambrosol as ambrosol hydrochloride) |
| **Route of Administration** | Oral |
| **Proposed Indication(s)** | Anti-psychotic |

**(b) Other Introductory information:**

AMBROSIA® Delayed-release Tablets are currently marketed in Australia as WONDERDRUG® Delayed-release Tablets. Applications have been submitted to the U.S. Food and Drug Administration (FDA) and to the European Medicines Agency (EMEA) at the same time as this submission to Health Canada. This submission is organized according to ICH's Common Technical Document (CTD) format.

Some of the submitted information makes reference to a 10 mg strength (e.g., P.8 Stability). The documentation on the 10 mg strength is provided as supporting documentation as it is only for the Australian market and is not proposed for the Canadian market.

Unless otherwise indicated, "N/A" in this document should be interpreted as "Not applicable".

## 2.3.S DRUG SUBSTANCE (AMBROSOL HYDROCHLORIDE, DRUGMAKER LTD.)

### 2.3.S.1 General Information (Ambrosol Hydrochloride, Drugmaker Ltd.)

#### *2.3.S.1.1 Nomenclature (Ambrosol Hydrochloride, Drugmaker Ltd.)*

**(a) Recommended International Non-proprietary name (INN):**

Ambrosol Hydrochloride (preferred name)

**(b) Compendial name, if relevant:**

N/A (drug substance does not appear in any compendia)

**(c) Chemical name(s):**

(1) 7-Fluoro-5-(2-(4-cyclobutyl)pyridinyl)-1,3-dihydro-3-hydroxy-2*H*-1,4-benzodiazepin-2-one (INN)

(2) 2*H*-1,4-benzodiazepin-2-one,7-Fluoro-5-(2-(4-cyclobutyl)pyridinyl)-1,3-dihydro-3-hydroxy- (USAN)

The INN is the preferred name and is consistent with chemical name as it appears in the Product Monograph.

**(d) Company or laboratory code:**

AH-1234

**(e) Other non-proprietary name(s) (e.g., national name, USAN, BAN):**

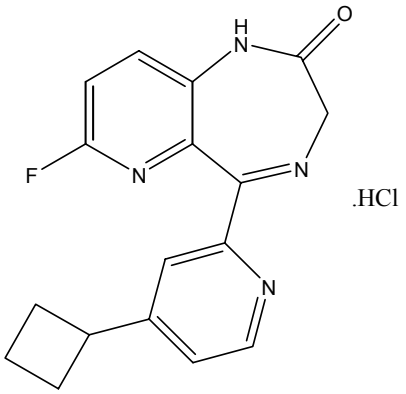
Ambrosol (USAN)

**(f) Chemical Abstracts Service (CAS) registry number:**

123456-78-9

***2.3.S.1.2 Structure (Ambrosol Hydrochloride, Drugmaker Ltd.)***

**(a) Structural formula, including relative and absolute stereochemistry:**



.HCl

**(b) Molecular formula:**

$C_{17}H_{14}N_4OF$ (base)
$C_{17}H_{14}N_4OF \bullet HCl$ (salt)

**(c) Molecular mass:**

309.32 (base)
345.78 (salt)

***2.3.S.1.3 General Properties (Ambrosol Hydrochloride, Drugmaker Ltd.)***

**(a) Physical description (e.g., appearance, colour, physical state):**

white to off-white, crystalline powder

**(b) Physical form (e.g., polymorphic form, solvate, hydrate):**

The drug substance can exist in two potential crystalline polymorphic forms. The preferred polymorphic form that was studied during clinical trials and to be used in routine production is "Form A" (melting point 143-145˚C). Further details relating to the investigations of other potential polymorphs are discussed in Module 2.3.S.3.1.

**(c) Solubilities (e.g., in common solvents, aqueous/nonaqueous solubility profile):**

*Solubility in common solvents (at 20° C):*

| Solvent | Solubility (mg/mL) | Descriptive Term (as defined in the USP) |
|---|---|---|
| water | 2.1 | Slightly soluble |
| propylene glycol | 84.0 | Soluble |
| glycerol | 3.8 | Slightly soluble |
| polysorbate 80 | 56.1 | Soluble |

*Quantitative aqueous pH solubility profile (at 37° C):*

| pH (of the buffer) | Solubility (mg/mL) | Descriptive Term (as defined in the USP) |
|---|---|---|
| 1.0 | 21.0 | Sparingly soluble (rapidly decomposes below pH 3) |
| 4.5 | 3.6 | Very slightly soluble |
| 6.5 | 0.12 | Very slightly soluble |
| 8.0 | 0.37 | Very slightly soluble |

*Calculation of dose/solubility volume:*

= largest dosage strength (mg) ÷ minimum concentration of drug (mg/mL) over the physiological pH range
= 75 mg ÷ 0.12 mg/mL
= 625 mL (i.e., >250 mL)

Therefore, Ambrosol HCl is not considered "highly soluble" according to the dose/solubility volume.

**(d) pH and pKa values:**

pH: 2.2, pKa: 5.8 (ref.: Merck Index, 12th Edition)

**(e) Other (e.g., partition coefficients, melting or boiling points, optical rotation, refractive index (for a liquid), hygroscopicity, UV absorption maxima and molar absorptivity):**

| | |
|---|---|
| Partition coefficient in octanol/water: | 0.3 at pH 2, 500 at pH 7, 900 at pH 7.4 |
| Melting point: | 143-145˚C (Form A) |
| Optical rotation: | -50˚ to -53˚ (2% (w/v) solution in 0.2 M HCl) |
| Hygroscopicity: | not hygroscopic |
| UV absorption maximum: | $UV_{max}$ = 369 nm |
| Molar absorptivity: | $\epsilon = 24400\ mol^{-1} \bullet L \bullet cm^{-1}$ |

**2.3.S.2 Manufacture (Ambrosol Hydrochloride, Drugmaker Ltd.)**

***2.3.S.2.1 Manufacturer(s) (Ambrosol Hydrochloride, Drugmaker Ltd.)***

**(a) Name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing:**

| Name and Address | Responsibility | Drug Master File Number |
|---|---|---|
| Drugmaker Ltd.<br>123 Main Street<br>City 1, Country A | all synthetic steps, micronization, and packaging | DMF 2005-1234 |
| Testy Inc.<br>789 High Road<br>City 3, Country C | testing of the drug substance<br>(i.e., particle size testing only) | N/A |
| Drugs 'R' Us<br>111 First Avenue<br>City 4, Country D | testing of the drug substance | N/A |

**(b) List of referenced Drug Master Files (DMFs) and DMF Numbers (copies of DMF letters of access should be located in Module 1):**

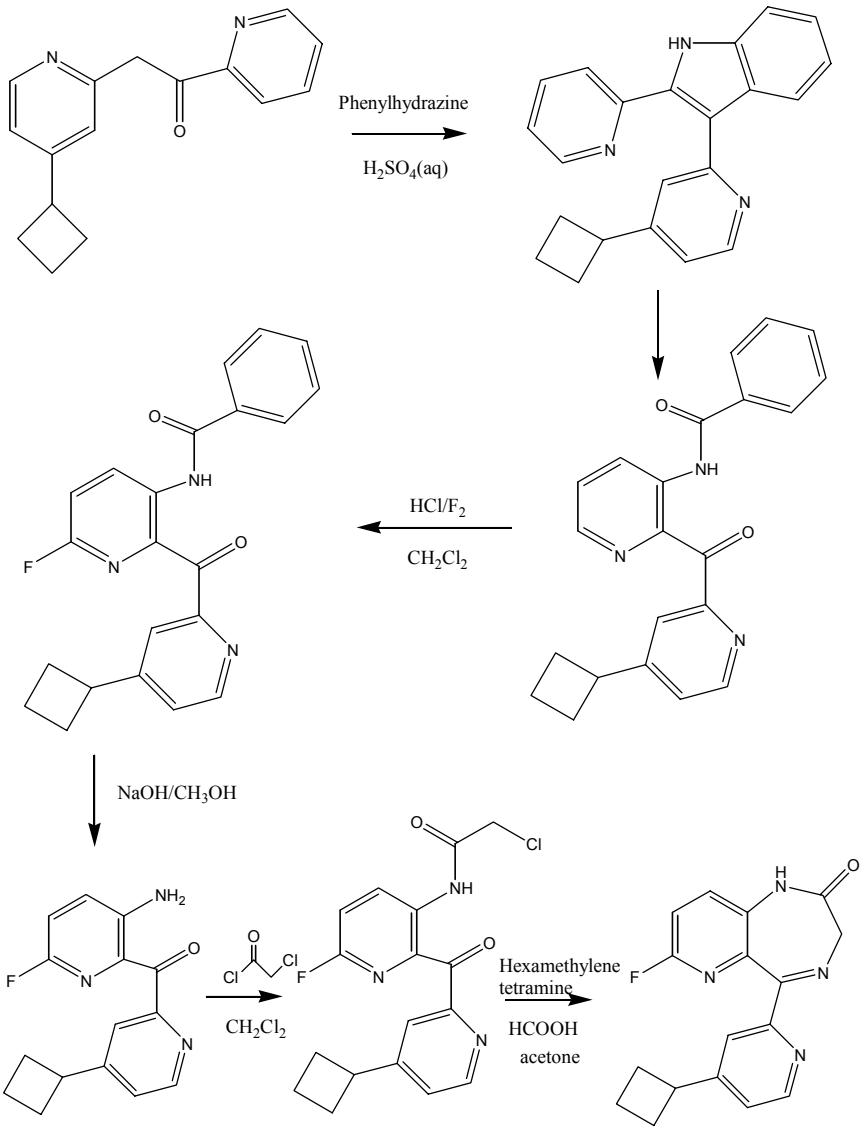
See above. It has been confirmed that DMF 2005-1234 has been received by Health Canada and that the necessary Cost Recovery Fees have been paid by the DMF Holder

Drugmaker Ltd. Where appropriate, information from the Open DMF has been reproduced in this submission and has been identified as such.

A copy of the Letter of Access for DMF 2005-1234 allowing access of Health Canada for this submission can be found in Module 1.2.6, page 4.

***2.3.S.2.2 Description of Manufacturing Process and Process Controls (Ambrosol Hydrochloride, Drugmaker Ltd.)***

**(a) Flow diagram of the synthetic process(es):**



The above information has been obtained from the "Open" portion of DMF 2005-1234. For further details on the proprietary information, please refer to the "Closed" portion of this DMF.

**(b) Brief narrative description of the manufacturing process(es):**

L-phenylalanine methyl ester hydrochloride has been chosen as the starting material as it is a commercially available compound, incorporates a significant structural fragment into the structure of the drug substance, and has undergone a number of organic synthetic steps in the preparation of the drug substance. Furthermore, potential impurities found in this compound have not been carried over to the final drug substance. Below is a narrative description of the manufacturing process for the drug substance.

1. L-phenylalanine methyl ester hydrochloride is dissolved in water and neutralized by adding aqueous potassium bicarbonate. Dichloromethane is then added to the solution. The solution is washed with water and dried over anhydrous magnesium sulfate.

2. N-benzyloxycarbonyl-L-aspartic acid-α-p-nitrophenyl, β-benzyl diester is added to the solution from Step 1. The mixture is kept at ambient temperature for 24 hours, and then heated to 65˚C for another 24 hours.

3. The mixture is cooled to ambient temperature, diluted with cyclohexane, and cooled to -18˚C for crystallization.

4. The crystalline product from Step 3 is isolated by filtration and dried to give β-benzyl N-benzyloxycarbonyl-L-aspartyl-L-phenylalanine methyl ester (Compound 5).

5. Compound 5 is dissolved in 75% acetic acid. Palladium black metal catalyst is added and the mixture is shaken with hydrogen at atmospheric pressure and ambient temperature for 12 hours.

6. The mixture is filtered to remove the catalyst, and the solvent is removed by distilling under reduced pressure.

7. The solid obtained in Step 6 is purified by recrystallizing from ethanol and dried under vacuum at 60˚C for 4 hours to give L-aspartyl-L-phenylalanine methyl ester (Compound 7).

8. The purified drug substance is micronized by air jet mill (Jet-O-Mizer) with the following operating conditions:
   Nozzles: Grinding (two in number): 100 psi each, Pushing: 75 psi
   Feeding rate: 50 g/min

The above information has been obtained from the "Open" portion of DMF 2005-1234. For further details on the proprietary information, please refer to the "Closed" portion of this DMF.

**(c) Alternate processes and explanation of their use:**

No alternate processes are proposed.

**(d) Reprocessing steps and justification:**

If the drug substance does not meet the purity limits, it may be recrystallized using the same procedure described in Step 7 above.

Any lots that undergo reprocessing (e.g., further recrystallization) will be added to the stability program.

***2.3.S.2.3 Control of Materials (Ambrosol Hydrochloride, Drugmaker Ltd.)***

**(a) Summary of the quality and controls of the materials (e.g., raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the drug substance:**

All raw materials used in the process meet the appropriate House (e.g., American Chemical Society (ACS)) standards.

Complete specifications for all raw materials and isolated intermediates can be found in Module 3.2.S.2.3, pages 50-75.

**(b) For drug substances or drug substance manufactured with reagents obtained from sources that are at risk of transmitting Bovine Spongiform Encephalopathy (BSE)/Transmissible Spongiform Encephalopathy (TSE) agents (e.g., ruminant origin), a letter of attestation (with supporting documentation) should be provided confirming that the material is not from a BSE/TSE affected country/area. A copy of the letter may be found in:**

N/A (neither the drug substance nor the reagents are obtained from sources that are at risk of transmitting BSE/TSE).

***2.3.S.2.4 Controls of Critical Steps and Intermediates (Ambrosol Hydrochloride, Drugmaker Ltd.)***

**(a) Summary of the controls performed at critical steps of the manufacturing process and on intermediates:**

| Critical Step or Intermediate | Test | Method Type | Acceptance Criteria |
|---|---|---|---|
| L-phenylalanine methyl ester hydrochloride (starting material) | Identification | HPLC | similar $R_t$ to standard |
| | Assay | HPLC | 85.0-115.0% (dried basis) |
| | Related Substances | HPLC | Individual impurity: NMT 0.5%<br>Total: NMT 1.0% |

| Critical Step or Intermediate | Test | Method Type | Acceptance Criteria |
|---|---|---|---|
| Compound 5 (isolated intermediate in Step 4) | Assay | HPLC | 90.0-110.0% |
| Compound 7 (following drying in Step 7) | Moisture Content | Karl Fischer | NMT 1.0% |

The above information has been obtained from the "Open" portion of DMF 2005-1234. For further details on the proprietary information, please refer to the "Closed" portion of this DMF.

***2.3.S.2.5 Process Validation and/or Evaluation (Ambrosol Hydrochloride, Drugmaker Ltd.)***

**(a) Description of process validation and/or evaluation studies (e.g., for aseptic processing and sterilization):**

N/A (not used for a sterile product).

***2.3.S.2.6 Manufacturing Process Development (Ambrosol Hydrochloride, Drugmaker Ltd.)***

**(a) Description and discussion of the significant changes made to the manufacturing process and/or manufacturing site of the drug substance used in producing nonclinical, clinical, comparative, stability, scale-up, pilot, and, if available, production scale batches:**

The batches used in toxicology studies and the early clinical studies were manufactured before the synthetic process was fully developed (Process C-01-002). The process has since been optimized to improve the overall yield with the addition of a purification step. Batches manufactured according to the updated/current process (Procedure C-01-003) are capable of meeting the proposed acceptance criteria (e.g., impurities).

**2.3.S.3 Characterisation (Ambrosol Hydrochloride, Drugmaker Ltd.)**

***2.3.S.3.1 Elucidation of Structure and other Characteristics (Ambrosol Hydrochloride, Drugmaker Ltd.)***

**(a) List of studies performed (e.g., IR, UV, NMR, MS, elemental analysis) and summary of the interpretation of evidence of structure:**

The structure of The drug substance has been confirmed by a series of studies including IR, UV, NMR, MS, and elemental analysis. Batch number GJC-2004-01 was used as the reference standard. The batch was manufactured using the same process as summarized in Module 2.3.S.2.2. The evidence of the molecular structure of Ambrosol HCl can be summarized as follows:

- The theoretical molecular formula for Ambrosol HCl is $C_{17}H_{14}N_4OF{\bullet}HCl$ (salt). Elemental analysis was performed and results compared with the % theoretical

composition.

- In the IR spectrum, all functional groups have been identified and all major bands are assigned.
- The UV spectrum of Ambrosol HCl contains absorption bands characteristic of cyclobutyl group and the benzodiazepine, providing evidence in support of the molecular structure of this compound.
- In the NMR spectra, all signals have been assigned and confirm the structure of Ambrosol HCl.
- The MS spectrum shows the expected molecular ion peaks and the high-resolution mass peak is in agreement with the expected mass.
- The X-ray crystal data are completely consistent with the proposed structure including absolute stereochemistry. A peak in the region of two theta = 6.3 in the XRD spectrum would indicate the presence of polymorphic Form B.

In summary, the proposed structure of Ambrosol HCl is in agreement with the spectral data and analytical data obtained. Copies of the spectra and full details on the interpretations can be found in Module 3.2.S.3.1, pages 5-25.

**(b) Discussion on the potential for isomerism and identification of stereochemistry (e.g., geometric isomerism, number of chiral centres and configurations):**

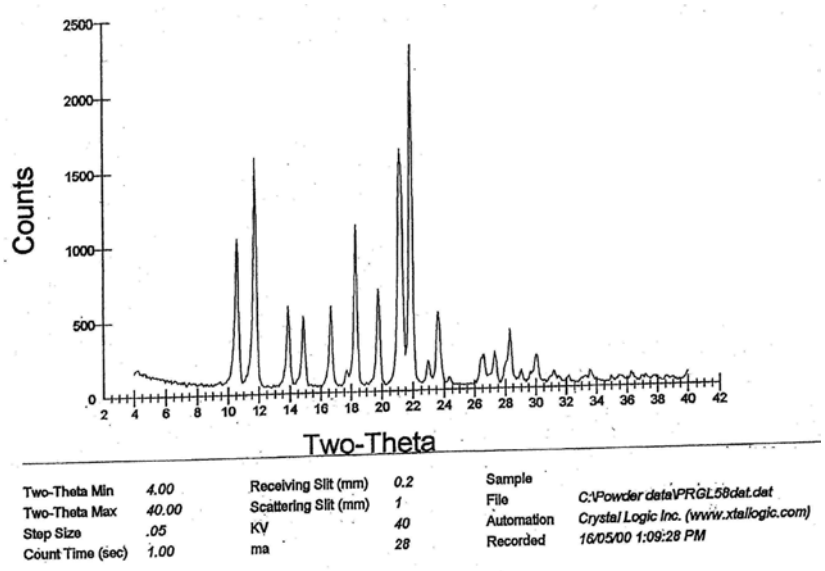
Ambrosol HCl is a stereochemically pure enantiomer with two chiral centres. The chiral carbon bonded to the cyclohexyl group is in R configuration. The stereogenic carbon in the azetidine is in S configuration. The hydroxyimino group is in Z configuration.

**(c) Summary of studies performed to identify potential polymorphic forms (including solvates):**

This drug substance can exist in two polymorphic forms which are differentiated by Differential Scanning Calorimetry (DSC) and X-ray Diffraction (XRD).

Recrystallization from ethanol yields Form A (mp about 143-145˚C); recrystallization from water yields Form B (mp about 137-139˚C). Form A was used in clinical trials and will be used in production due to its superior thermal stability. The aqueous solubilities of the two polymorphs are essentially the same, at 95 mg/mL (Form A) and 105 mg/mL (Form B).

The presence of Form A in the commercial material is routinely controlled in the drug substance specification by the XRD test (limit: Form B NMT 5.0%). Following is a sample pattern indicating the ability of detecting the presence of the preferred polymorph. House XRD Method TM-DS-02, ver. 1.0 is used for the analyses of the polymorphic content and copies of the method and validation report can be found in Modules 3.2.S.4.2 (pages 2-8) and 3.2.4.3 (pages 2-20), respectively.




**(d) Summary of studies performed to identify the particle size distribution of the drug substance:**

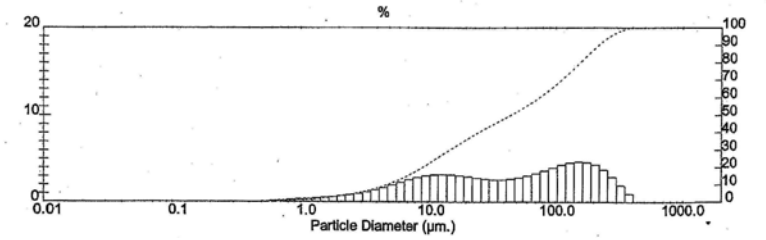
The particle size distribution of several batches was characterized by laser diffraction. Below is a summary of the results obtained as well as a typical diffraction pattern (Batch No. G123).

| Parameter | Acceptance Criteria | Batch Number (and use) | | |
|---|---|---|---|---|
| | | G123 (nonclinical) | J456 (clinical and stability studies) | C789 (clinical and stability studies) |
| D (v, 0.1) | NLT 1.5 µm | 3.2 µm | 2.3 µm | 2.8 µm |
| D (v, 0.5) | 4.0 to 8.0 µm | 6.4 µm | 5.1 µm | 5.3 µm |
| D (v, 0.9) | NMT 20 µm | 17.0 µm | 14.5 µm | 15.1 µm |

**Result Statistics**

| | | | |
|---|---|---|---|
| Distribution Type: Volume | Concentration = 0.0193 %Vol | Density = 1.000 g / cub. cm | Specific S.A. = 0.5524 sq. m / g |
| Mean Diameters: | D (v, 0.1) = 4.83 um | D (v, 0.5) = 44.46 um | D (v, 0.9) = 217.65 um |
| D [4, 3] = 82.00 um | D [3, 2] = 10.86 um | Span = 4.786E+00 | Uniformity = 1.510E+00 |

| Size (um) | Volume Under % | Size (um) | Volume Under % | Size (um) | Volume Under % | Size (um) | Volume Under % |
|---|---|---|---|---|---|---|---|
| 0.055 | 0.00 | 0.635 | 0.40 | 7.31 | 15.96 | 84.15 | 62.86 |
| 0.061 | 0.00 | 0.700 | 0.50 | 8.06 | 17.69 | 92.79 | 65.28 |
| 0.067 | 0.00 | 0.772 | 0.63 | 8.89 | 19.51 | 102.3 | 67.83 |
| 0.074 | 0.00 | 0.851 | 0.78 | 9.80 | 21.43 | 112.8 | 70.53 |
| 0.082 | 0.00 | 0.938 | 0.97 | 10.81 | 23.41 | 124.4 | 73.35 |
| 0.090 | 0.00 | 1.03 | 1.17 | 11.91 | 25.43 | 137.2 | 76.25 |
| 0.099 | 0.00 | 1.14 | 1.42 | 13.14 | 27.47 | 151.3 | 79.22 |
| 0.109 | 0.00 | 1.26 | 1.69 | 14.49 | 29.52 | 166.8 | 82.21 |
| 0.121 | 0.00 | 1.39 | 1.99 | 15.97 | 31.54 | 183.9 | 85.17 |
| 0.133 | 0.01 | 1.53 | 2.32 | 17.62 | 33.53 | 202.8 | 88.03 |
| 0.147 | 0.01 | 1.69 | 2.68 | 19.42 | 35.46 | 223.6 | 90.73 |
| 0.162 | 0.01 | 1.86 | 3.08 | 21.42 | 37.33 | 246.6 | 93.17 |
| 0.178 | 0.02 | 2.05 | 3.52 | 23.62 | 39.15 | 271.9 | 95.31 |
| 0.196 | 0.02 | 2.26 | 3.99 | 26.04 | 40.90 | 299.8 | 97.06 |
| 0.217 | 0.03 | 2.49 | 4.52 | 28.72 | 42.60 | 330.6 | 98.40 |
| 0.239 | 0.04 | 2.75 | 5.10 | 31.68 | 44.27 | 364.6 | 99.41 |
| 0.263 | 0.05 | 3.03 | 5.74 | 34.92 | 45.91 | 402.0 | 99.97 |
| 0.290 | 0.07 | 3.34 | 6.46 | 38.50 | 47.55 | 443.3 | 100.00 |
| 0.320 | 0.09 | 3.69 | 7.26 | 42.45 | 49.20 | 488.8 | 100.00 |
| 0.353 | 0.11 | 4.07 | 8.16 | 46.81 | 50.90 | 539.0 | 100.00 |
| 0.389 | 0.13 | 4.48 | 9.16 | 51.62 | 52.65 | 594.3 | 100.00 |
| 0.429 | 0.16 | 4.94 | 10.27 | 56.92 | 54.47 | 655.4 | 100.00 |
| 0.473 | 0.20 | 5.45 | 11.50 | 62.76 | 56.40 | 722.7 | 100.00 |
| 0.522 | 0.25 | 6.01 | 12.87 | 69.21 | 58.43 | 796.9 | 100.00 |
| 0.576 | 0.31 | 6.63 | 14.35 | 76.32 | 60.58 | 878.7 | 100.00 |



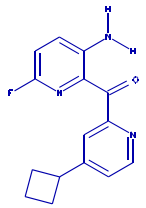
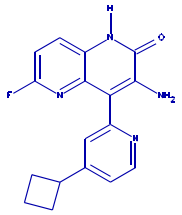

**(e) Other characteristics:**

Ambrosia hydrochloride is not hygroscopic and there have not been any hydrated forms observed or reported for this material. Therefore, the potential for conversion to hydrated forms of the drug substance is not a concern. In addition, the drug substance is not converted to a hydrated form during the aqueous wet granulation for the drug product manufacturing process.

***2.3.S.3.2 Impurities (Ambrosol Hydrochloride, Drugmaker Ltd.)***

**(a) Identification of potential and actual impurities arising from the synthesis, manufacture and/or degradation:**

**(i) List of drug-related impurities (e.g., starting materials, by-products, intermediates, chiral impurities, degradation products), including chemical name, structure, and origin:**

| Drug-related Impurity (chemical name or descriptor) | Structure | Origin |
|---|---|---|
| RC1:<br>cyclobutyl-fluoro-amino-dipyridylketone |  | Synthetic intermediate (Step 4). |
| RC2:<br>3-amino-6-fluoro-4-(2-pyridyl)carbo-N-2-styril |  | Potential degradation product / metabolite (ref. Product Monograph for Ambrosia® Delayed-release Tablets (Module 1.3.1, page 657)). |

**(ii) List of process-related impurities (e.g., residual solvents, reagents), including compound name and step used in synthesis:**

Step 1: Dichloromethane
Step 3: Cyclohexane
Step 5: Acetic Acid
Step 5: Palladium black metal catalyst
Step 7: Ethanol (final purification solvent)

**(b) Basis for setting the acceptance criteria for impurities:**

**(i) Maximum daily dose (i.e., the amount of drug substance administered per day), ICH Reporting/Identification/Qualification Thresholds for drug-related impurities, and Concentration Limits (ppm) for process-related impurities (e.g., residual solvents):**

| **Maximum Daily Dose:** | **75 mg** | |
|---|---|---|
| **Test** | **Parameter** | **ICH Threshold or Concentration Limit** |
| Related impurities<br>(ref. ICH Q3A(R)) | Reporting Threshold | 0.05% |
| | Identification Threshold | 0.10% |
| | Qualification Threshold | 0.15% |

| | | |
|---|---|---|
| Residual solvents (ref. ICH Q3C) | Dichloromethane | 600 ppm (PDE 6.0 mg/day) |
| | Cyclohexane | 3880 ppm (PDE 38.0 mg/day) |
| | Acetic Acid | 5000 ppm (PDE 50.0 mg/day) |
| | Ethanol | 5000 ppm (PDE 50.0 mg/day) |

**(ii) Data on observed impurities for relevant batches (e.g., nonclinical, clinical, and comparative):**

| **Impurity (drug-related and process-related)** | **Acceptance Criteria** | **Results (include batch number* and use) (e.g., nonclinical, clinical, comparative)** | | |
|---|---|---|---|---|
| | | Lot G123 (nonclinical) | Lot J456 (clinical and stability studies) | Lot C789 (clinical and stability studies) |
| RC1 | NMT 0.15% | 0.11% | 0.06% | 0.08% |
| RC2 | NMT 0.3% | 0.20% | 0.23% | 0.16% |
| Maximum individual unspecified impurity | NMT 0.10% | 0.06% (RRT 3.2 min.) | 0.07% (RRT 3.2 min.) | 0.05% (RRT 3.2 min.) |
| Total impurities | NMT 0.6% | 0.4% | 0.4% | 0.3% |
| Dichloromethane | NMT 600 ppm | 89 ppm | 101 ppm | 81 ppm |
| Cyclohexane | NMT 3880 ppm | 120 ppm | 132 ppm | 119 ppm |
| Acetic Acid | NMT 5000 ppm | 340 ppm | 380 ppm | 360 ppm |
| Ethanol | NMT 5000 ppm | 480 ppm | 510 ppm | 460 ppm |
| Residual Palladium | (not routinely tested) | <LOD (0.5 ppm) | <LOD (0.5 ppm) | <LOD (0.5 ppm) |

RRT = relative retention time
LOD = limit of detection

*** include strength, if reporting impurity levels found in the drug product (e.g., for comparative studies)**

**(iii) Justification of proposed acceptance criteria for impurities:**

In summary, the new drug substance specification includes the following controls for impurities:

*Organic Impurities*

- a limit for the "specified identified impurity" RC1 with an acceptance criterion of NMT 0.15% corresponding to the ICH Qualification Threshold; since the proposed limit corresponds to the ICH Qualification

Threshold, additional qualification is not considered necessary;
- a limit for the "specified identified impurity" RC2 with an acceptance criterion of NMT 0.3%; the limit of NMT 0.3% is considered qualified as RC2 is a known metabolite as listed in the Product Monograph (Module 1.3.1, page 657) and in published literature (A. Brightspark, et.al., *Pharmacology of Human Drugs*, (1999) 28(5), p 345-345) (Module 3.3, pages 30-45);
- a limit for "any unspecified impurity" with an acceptance criterion of NMT 0.10% corresponding to the ICH Identification Threshold;
- a limit of NMT 0.6% for "Total Impurities" based on the results observed from the batch analyses (approx. 0.4%).

*Residual Solvents*

- acceptance criteria for the residual solvents that are in accordance with the thresholds for the relevant solvent from ICH's Q3C guideline.

*Inorganic Impurities*

- the USP Heavy Metals test (USP <231>, Method II) has been included with an acceptance criterion of NMT 10 ppm;
- six production scale batches of the drug substance were tested for Palladium residue by Inductively Coupled Plasma - Atomic Emission Spectrometry (ICP-AES); results for all batches were less than the limit of detection (<0.5 ppm) (see Module 3.2.S.4.4, page 67 for details of the analysis); therefore, it was concluded that as no Palladium was detected, routine testing is not warranted.

## 2.3.S.4 Control of the Drug Substance (Ambrosol Hydrochloride, Drugmaker Ltd.)

### *2.3.S.4.1 Specification (Ambrosol Hydrochloride, Drugmaker Ltd.)*

**(a) Specification for the drug substance:**

| **Standard Claimed (e.g., Professed, House, USP, BP, Ph.Eur.)** | | Professed |
|---|---|---|
| **Specification Reference Number and/or Version** | | TS-DS-004 (April 1, 2004) |
| **Test** | **Acceptance Criteria** | **Analytical Procedure (Type/Source/Version)** |
| Description | white to off white crystalline powder | Visual/SOP 123, ver. 1.0 |
| Identification | A: IR conforms to standard<br>B: XRD conforms to standard<br>C: positive for chloride | A: IR/House/TM-DS-01, ver. 1.0<br>B: XRD/House/TM-DS-02, ver. 1.0<br>C: USP <191> |
| Optical Rotation<br>$[\alpha]_D^{20}$ | -50˚ to -53˚<br>(2% (w/v) solution in 0.2 M HCl) | Polarimetry/House/TM-DS-06, ver. 1.0 |
| Residue on Ignition | NMT 0.1% | USP <281> |
| Heavy Metals | NMT 10 ppm | USP <231>, Method II |

| Standard Claimed (e.g., Professed, House, USP, BP, Ph.Eur.) | | Professed |
|---|---|---|
| **Specification Reference Number and/or Version** | | TS-DS-004 (April 1, 2004) |
| **Test** | **Acceptance Criteria** | **Analytical Procedure (Type/Source/Version)** |
| pH | 3.7 to 5.2 | USP |
| Water Content | NMT 0.5% | Karl Fischer titration |
| Polymorphic Content | Form B: NMT 5.0% | XRD/House/TM-DS-02, ver. 1.0 |
| Particle Size | D (v, 0.1) NLT 1.5 µm<br>D (v, 0.5) 4.0 to 8.0 µm<br>D (v, 0.9) NMT 20 µm | Laser diffraction/House/TM-DS-04, ver. 1.0 |
| Related Substances | RC1: NMT 0.15%<br>RC2: NMT 0.3%<br>Individual unspecified: NMT 0.10%<br>Total: NMT 0.6% | HPLC/House/TM-DS/DP-05, ver. 2.0 |
| Residual Solvents | Dichloromethane NMT 600 ppm<br>Cyclohexane NMT 3880 ppm<br>Acetic Acid NMT 5000 ppm<br>Ethanol NMT 5000 ppm | GC/House/TM-DS-04, ver. 1.0 |
| Assay | 98.0-102.0% Ambrosol (dried basis) | HPLC/House/TM-DS/DP-03, ver. 1.1 |

A copy of the signed and dated specification TS-DS-004 (April 1, 2004) can be found in Module 3.2.S.4.1, pages 2-5.

### *2.3.S.4.2 Analytical Procedures (Ambrosol Hydrochloride, Drugmaker Ltd.)*

**(a) Summary of the analytical procedures (e.g., key method parameters, conditions, system suitability testing):**

Due to the length of information, summaries of the following House analytical methods are attached to this Quality Overall Summary:

| Attachment | Summary | Analytical Procedure |
|---|---|---|
| 1 | method | Assay: HPLC/House/TM-DS/DP-03, ver. 1.1 |
| 3 | method | Related Substances: HPLC/House/TM-DS/DP-05, ver. 2.0 |
| 5 | method | Residual Solvents: GC/House/TM-DS-04, ver. 1.0 |
| 7 | method | Polymorphic Content: XRD/House/TM-DS-02, ver. 1.0 |

### *2.3.S.4.3 Validation of Analytical Procedures (Ambrosol Hydrochloride, Drugmaker Ltd.)*

**(a) Summary of the validation information (e.g., validation parameters and results):**

Due to the length of information, summaries of the validation reports for the following House analytical methods are attached to this Quality Overall Summary:

| Attachment | Summary | Analytical Procedure |
|---|---|---|
| 2 | validation report | Assay: HPLC/House/TM-DS/DP-03, ver. 1.1 |
| 4 | validation report | Related Substances: HPLC/House/TM-DS/DP-05, ver. 2.0 |
| 6 | validation report | Residual Solvents: GC/House/TM-DS-04, ver. 1.0 |
| 8 | validation report | Polymorphic Content: XRD/House/TM-DS-02, ver. 1.0 |

***2.3.S.4.4 Batch Analyses (Ambrosol Hydrochloride, Drugmaker Ltd.)***

**(a) Description of the batches:**

| Batch Number | Batch Size | Date and Site of Production | Use (e.g., nonclinical, clinical, comparative) |
|---|---|---|---|
| Lot G123 | Pilot (20 Kg) | 01/01/2004, Drugmaker Ltd., City 1, Country A | nonclinical |
| Lot J456 | Production (100 Kg) | 04/01/2004, Drugmaker Ltd., City 1, Country A | clinical and stability studies |
| Lot C789 | Production (100 Kg) | 04/01/2004, Drugmaker Ltd., City 1, Country A | clinical and stability studies |

**(b) Summary of results for relevant batches (e.g., nonclinical, clinical, comparative):**

| Test | Acceptance Criteria | Results | | |
|---|---|---|---|---|
| | | Lot G123 (nonclinical) | Lot J456 (clinical and stability studies) | Lot C789 (clinical and stability studies) |
| Description | white to off white crystalline powder | white to off white crystalline powder | white to off white crystalline powder | white to off white crystalline powder |
| Identification | A: IR conforms to std.<br>B: XRD conforms to std.<br>C: positive for $Cl^-$ | A: conforms to std.<br>B: conforms to std.<br>C: positive for $Cl^-$ | A: conforms to std.<br>B: conforms to std.<br>C: positive for $Cl^-$ | A: conforms to std.<br>B: conforms to std.<br>C: positive for $Cl^-$ |
| Optical Rotation $[\alpha]_D^{20}$ | -50˚ to -53˚ (2% (w/v) solution in 0.2 M HCl) | -53˚ | -51˚ | -52˚ |
| Residue on Ignition | NMT 0.1% | <0.1% | <0.1% | <0.1% |
| Heavy Metals | NMT 10 ppm | <10 ppm | <10 ppm | <10 ppm |
| pH | 3.7 to 5.2 | 4.2 | 4.8 | 4.1 |
| Water Content | NMT 0.5% | 0.3% | 0.1% | 0.3% |

| Test | Acceptance Criteria | Results | | |
|---|---|---|---|---|
| | | **Lot G123 (nonclinical)** | **Lot J456 (clinical and stability studies)** | **Lot C789 (clinical and stability studies)** |
| Polymorphic Content | Form B: NMT 5.0% | 2.8% | 3.2% | 2.1% |
| Particle Size | D (v, 0.1) NLT 1.5 µm<br>D (v, 0.5) 4.0 to 8.0 µm<br>D (v, 0.9) NMT 20 µm | see discussion of results in Module 2.3.S.3.1 | | |
| Related Substances | RC1: NMT 0.15%<br>RC2: NMT 0.3%<br>Ind. unsp.: NMT 0.10%<br>Total: NMT 0.6% | see discussion of results in Module 2.3.S.3.2 | | |
| Residual Solvents | $CH_2Cl_2$ NMT 600 ppm<br>Cyclohexane 3880 ppm<br>Acetic Acid 5000 ppm<br>EtOH NMT 5000 ppm | see discussion of results in Module 2.3.S.3.2 | | |
| Assay | 98.0-102.0% Ambrosol (dried basis) | 99.9% | 99.5% | 100.1% |

Copies of the certificates of analyses for the above lots can be found in Module 3.2.S.4.4, page 2-10.

**(c) Summary of analytical procedures and validation information for those procedures not previously summarized in 2.3.S.4.2 and 2.3.S.4.3 (e.g., historical analytical procedures):**

N/A (there were not any historical methods used to support the submission).

***2.3.S.4.5 Justification of Specification (Ambrosol Hydrochloride, Drugmaker Ltd.)***

**(a) Justification of the drug substance specification (e.g., evolution of tests, analytical procedures, and acceptance criteria, differences from compendial standard):**

The ICH Q6A guideline has been consulted for the development of the drug substance specification. The standard “Universal Tests” (i.e., Description, Identification, Assay, and Impurities) have been included.

The justification for the proposed acceptance criteria for the Impurities tests (Related Substances and Residual Solvents) has been previously discussed (see Module 2.3.S.3.2).

Additional "Specific Tests" have been included which are common to this type of drug substance:

- Particle Size: a test for particle size is included in the proposed specification as Ambrosol HCl is not considered “highly soluble” according to the dose/solubility volume calculation and to ensure consistent micronized material, the acceptance criteria are based on the results for the material used in the clinical studies, in addition, the ranges are based on the precision of the method as determined

during validation;
- Polymorphs: the XRD spectrum (Identification Test B) will control for Polymorphic Form A, a limit of NMT 5.0% for Polymorphic Form B is included in the specification and is considered qualified based on the results observed for the material used for clinical studies;
- other standard tests (e.g., Residue on Ignition, Heavy Metals, pH, and Water Content) have been included with acceptance criteria consistent with the various pharmacopoeia.

These tests are believed to control the quality of the material and ensure its suitability of use in the manufacture of the drug product.

**2.3.S.5 Reference Standards or Materials (Ambrosol Hydrochloride, Drugmaker Ltd.)**

**(a) Source of reference standards or reference materials (e.g., House, USP, BP, Ph.Eur.):**

An in-house reference standard has been used (batch number GJC-2004-01).

**(b) Characterization and evaluation of non-official (e.g., non-compendial) reference standards or reference materials (e.g., method of manufacture, elucidation of structure, certificate of analysis, calibration against an official standard):**

Batch number GJC-2004-01 was manufactured using the same process as summarized in Module 2.3.S.2.2. Full characterization of the structure of the material has been performed which included IR, UV, NMR ($^{1}H$ and $^{13}C$), MS, and elemental analysis studies.

A copy of the certificate of analysis for Batch number GJC-2004-01 can be found in Module 3.2.S.5, page 10. All tests in the currently proposed drug substance specification were performed and the results met the proposed acceptance criteria.

**2.3.S.6 Container Closure System (Ambrosol Hydrochloride, Drugmaker Ltd.)**

**(a) Description of the container closure system(s) for the storage and shipment of the drug substance:**

Fibreboard drum lined with two polyethylene bags (LD-type). The fibreboard lid is secured with a metal O-ring.

**(b) Other information on the container closure system(s):**

The materials used in the container closure system are considered acceptable for use in foods.

**2.3.S.7 Stability (Ambrosol Hydrochloride, Drugmaker Ltd.)**

***2.3.S.7.1 Stability Summary and Conclusions (Ambrosol Hydrochloride, Drugmaker Ltd.)***

**(a) Summary of stress testing (e.g., heat, humidity, oxidation, photolysis, acid/base): and results:**

| Stress Condition | Treatment | Observations |
|---|---|---|
| heat | 60°C for 4 weeks in a petri dish | Assay: 95.5%<br>RC1: 0.1%<br>RC2: 3.0%<br>Total unspecified:0.5 %<br>Total impurities: 4.0% |
| humidity | 50°C / 80% RH | Assay: 97.6%<br>RC1: 0.1%<br>RC2: 1.5%<br>Total unspecified: 0.5%<br>Total impurities: 2.3% |
| oxidation | oxygen bubbled through 1 g/mL aqueous solution for 8 hours | Assay: 98.8%<br>RC1: 0.1%<br>RC2: 0.5%<br>Total unspecified: 0.4%<br>Total impurities: 1.1% |
| photolysis | 600 footcandles (FC) for 4 weeks in a petri dish | Assay: 88.2%<br>RC1: 0.1%<br>RC2: 7.2%<br>Total unspecified: 3.0%<br>Total impurities: 11.5% |
| acid | 1 g/mL in 0.1N HCl at ambient temperature for 1 hour | Assay: 86.3%<br>RC1: 0.1%<br>RC2: 9.1%<br>Total unspecified: 3.2 %<br>Total impurities: 12.5% |
| base | 1 g/mL in 0.1N NaOH at ambient temperature for 8 hours | Assay: 99.7%<br>RC1 and RC2: Not Detected<br>Total unspecified: 0.1%<br>Total impurities: 0.2% |

The above stress study results illustrate that the proposed method for related substances (HPLC/House/TM-DS-05, ver. 2.0) is stability indicating and specific for the detection of potential degradation products by the demonstrated observance of mass balance. In addition, the method was shown to be capable of detecting potential unspecified degradation products (which did not interfere with peaks for the drug substance or impurities RC1 and RC2).

Based on the results of the above stress study, it appears the drug substance, Ambrosol HCl, is susceptible to degradation when exposed to light and acid conditions. As such, the material should be stored in opaque containers, protected from light.

**(b) Summary of accelerated and long term testing (e.g., studies conducted, protocols used, results obtained):**

Accelerated and long term stability studies were conducted in accordance with the ICH

Q1A(R2) guideline. Following is a summary of the study details (the container closure system used for the studies was the same as described in Module 2.3.S.6):

| Storage Conditions | Batch Number | Batch Size | Completed (and Proposed) Test Intervals |
|---|---|---|---|
| 25˚C/60% RH<br>40˚C/75% RH | Lot G123 | Pilot (20 Kg) | 0, 3, 6, 9, 12, (18, 24, 36)<br>0, 1, 3, 6 |
| 25˚C/60% RH<br>40˚C/75% RH | Lot J456 | Production (100 Kg) | 0, 3, 6, 9, 12, (18, 24, 36)<br>0, 1, 3, 6 |
| 25˚C/60% RH<br>40˚C/75% RH | Lot C789 | Production (100 Kg) | 0, 3, 6, 9, 12, (18, 24, 36)<br>0, 1, 3, 6 |

The following tests were performed and results obtained:

| Test | Results/Observations |
|---|---|
| Description | - conforms to spec (white to off white crystalline powder) |
| Assay | - results ranged between 99.0-101.1%,<br>no trends or variability were observed (spec: 98.0-102.0%) |
| Related Substances | - slight increase in the concentration of RC2 from 0.1% to 0.2% under accelerated condition (results under the long term condition were consistently approx. 0.1% for RC2),<br>- the concentration of RC1 was consistently <0.15% (confirming that it is not a potential degradation product),<br>- no new unspecified degradation products were detected,<br>- total impurities increased from 0.2% to 0.4% under the accelerated condition (no increase was observed under the long term condition),<br>- no variability in the data was observed |
| pH | - consistently between 4.2 to 4.9 (spec: 3.7 to 5.2) |
| Water Content | - slight increase in moisture content from 0.2% to 0.3% when stored under the accelerated conditions only |

In accordance with ICH's Q1E guideline, the stability data obtained to date (i.e., 12 months at 25˚C/60% RH and 6 months at 40˚C/75% RH) is believed to support the proposed re-test period of 24 months when stored in the proposed container closure system under the recommended storage conditions.

**(c) Proposed storage conditions and re-test period (or shelf life, as appropriate):**

| Container Closure System | Storage Conditions | Re-test Period |
|---|---|---|
| Fibreboard drum containing two LDPE bags (lid is secured with a metal O-ring) | Store at controlled room temperature (15 to 30˚C) | 24 months |

***2.3.S.7.2 Post-approval Stability Protocol and Stability Commitment (Ambrosol Hydrochloride, Drugmaker Ltd.)***

**(a) Stability protocol for commitment batches (e.g., storage conditions (including tolerances), testing frequency, number of batches and batch sizes, container closure system(s), tests and acceptance criteria):**

As the primary stability studies included two production scale baches (Lots J456 and C789), the studies on these batches will continue to beyond the proposed re-test period of 24 months. One additional production scale batch will be added to the stability program and will be tested to beyond the proposed re-test period.

Following is a summary of the protocol details for the commitment batches:

| Protocol Parameter | Description | |
|---|---|---|
| Storage conditions | 25±2˚C, 60±5% RH | |
| Testing frequency / Batches | Lots J456 and C789: 18, 24, 36 months<br>one additional production scale batch: 0, 3, 6, 9, 12, 18, 24, 36 months | |
| Container closure system(s) | Same as described in Module 2.3.S.6 | |
| Tests and acceptance criteria | Description | white to off white crystalline powder |
| | Assay | 98.0-102.0% |
| | Related Substances | RC2: NMT 0.3%<br>Any unspecified NMT 0.10%<br>Total: NMT 0.6% |
| | pH | 3.7 to 5.2 |
| | Water Content | NMT 0.5% |

***2.3.S.7.3 Stability Data (Ambrosol Hydrochloride, Drugmaker Ltd.)***

**(a) The actual stability results (i.e., raw data) should be provided in Module 3.**

The actual stability results (i.e., raw data) can be found in Module 3.2.S.7.3, pages 2-25.

**(b) Summary of analytical procedures and validation information for those procedures not previously summarized in 2.3.S.4 (e.g., analytical procedures used only for stability studies):**

N/A (there were not any historical methods used to support the submission).

## 2.3.P DRUG PRODUCT (AMBROSIA® DELAYED-RELEASE TABLETS, EC Tablets)

### 2.3.P.1 Description and Composition of the Drug Product (Ambrosia® Delayed-release Tablets, EC Tablets)

**(a) Description of the dosage form:**

The proposed drug product is available in three strengths of 25 mg (red), 50 mg (yellow), and 75 mg (blue) as round, biconvex, film (enteric) coated tablets.

**(b) Composition of the dosage form:**

**(i) Composition, i.e., list of all components of the dosage form, and their amounts on a per unit basis (including overages, if any):**

| Component and Quality Standard (and Grade, if applicable) | Function | Strength (label claim, as base) | | | | | |
|---|---|---|---|---|---|---|---|
| | | 25 mg (base) | | 50 mg (base) | | 75 mg (base) | |
| | | Quantity per unit | % | Quantity per unit | % | Quantity per unit | % |
| ***Tablet Core*** | | | | | | | |
| Ambrosol HCl, Professed[a] | active[a] | 30.0 mg | 30.0% | 60.0 mg | 30.0% | 90.0 mg | 30.0% |
| Microcrystalline Cellulose, NF (Avicel PH-102) | filler/binder/ disintegrant | 55.0 mg | 55.0% | 110.0 mg | 55.0% | 165.0 mg | 55.0% |
| Povidone, USP (PVP-K 30) | binder/ disintegrant | 9.0 mg | 9.0% | 18.0 mg | 9.0% | 27.0 mg | 9.0% |
| Crospovidone, NF | disintegrant | 5.0 mg | 5.0% | 10.0 mg | 5.0% | 15.0 mg | 5.0% |
| Magnesium Stearate, NF | lubricant | 0.8 mg | 0.8% | 1.6 mg | 0.8% | 2.4 mg | 0.8% |
| Purified Water, USP[b] | granulat. fluid | -- | (--) | -- | (--) | -- | (--) |
| Colloidal Silicon Dioxide, NF (Cab-O-Sil) | glidant | 0.2 mg | 0.2% | 0.4 mg | 0.2% | 0.6 mg | 0.2% |
| *Core weight* | | 100.0 mg | 100.0% | 200.0 mg | 100.0% | 300.0 mg | 100.0% |
| ***Coating (10% weight gain)*** | | ***% coating solution*** | | | | | |
| Methacrylic Acid Copolymer (Type C), NF | enteric coating agent | 7.0 mg | 7.0% | 14.0 mg | 7.0% | 21.0 mg | 7.0% |
| Polyethylene Glycol, NF | plasticizer | 0.5 mg | 0.5% | 1.0 mg | 0.5% | 1.5 mg | 0.5% |
| Triethyl Citrate, NF | plasticizer | 0.5 mg | 0.5% | 1.0 mg | 0.5% | 1.5 mg | 0.5% |
| Talc, USP | opacifier | 0.5 mg | 0.5% | 1.0 mg | 0.5% | 1.5 mg | 0.5% |
| Titanium Dioxide, USP | opacifier | 0.5 mg | 0.5% | 1.0 mg | 0.5% | 1.5 mg | 0.5% |
| FD&C Red No. 4, House | colourant | 1.0 mg | 1.0% | -- | -- | -- | -- |
| D&C Yellow No.10, House | colourant | -- | -- | 2.0 mg | 1.0% | -- | -- |
| FD&C Blue No. 2, House | colourant | -- | -- | -- | -- | 3.0 mg | 1.0% |
| Purified Water, USP[b] | solvent | -- | qs 100% | -- | qs 100% | -- | qs 100% |
| ***Printing*** | | | | | | | |

| Component and Quality Standard (and Grade, if applicable) | Function | Strength (label claim, as base) | | | | | |
|---|---|---|---|---|---|---|---|
| | | 25 mg (base) | | 50 mg (base) | | 75 mg (base) | |
| | | Quantity per unit | % | Quantity per unit | % | Quantity per unit | % |
| Superwhite® Printing Ink, House | printing ink | trace | trace | trace | trace | trace | trace |
| ***Total (excluding water)***[b] | | 110.0 mg | | 220.0 mg | 0.5% | 330.0 mg | 100.0% |

[a] Each tablet contains 1.0 mg of Ambrosol (active base) per 1.2 mg of Ambrosol HCl (salt).
[b] Purified Water, used in the granulation and coating solutions, is removed during drying process.

**(ii) Composition of all *components that are mixtures* (e.g., colourants, coatings, capsule shells, imprinting inks):**

Superwhite® Printing Ink, containing shellac and lecithin, is a pharmaceutical air drying liquid ink for application by offset gravure printers ("pill printers") onto pharmaceutical capsules and tablets.

For additional information (e.g., quantitative compositions), please refer to DMF 2005-5678 from Colourbuster Inc. A copy of the Letter of Access for DMF-2005-5678 allowing access of Health Canada for this submission can be found in Module 1.2.6.

**(c) Description of accompanying reconstitution diluent(s), if applicable:**

N/A (there are not any accompanying diluents).

**(d) Type of container closure system used for the dosage form and accompanying reconstitution diluent, if applicable:**

The product will be available in HDPE bottles of 100's and unit dose PVC/Aluminum foil blisters (5x10's).

## 2.3.P.2 Pharmaceutical Development (Ambrosia® Delayed-release Tablets, EC Tablets)

### *2.3.P.2.1 Components of the Drug Product (Ambrosia® Delayed-release Tablets, EC Tablets)*

#### *2.3.P.2.1.1 Drug Substance (Ambrosia® Delayed-release Tablets, EC Tablets)*

**(a) Discussion of the:**

**(i) compatibility of the drug substance with excipients listed in 2.3.P.1:**

The drug substance has a slight incompatibility with lactose, especially when used in a wet granulation process. Hence, in all subsequent lots lactose was replaced with microcrystalline cellulose. The compatibility studies indicated the finally chosen excipients and manufacturing process

were suitable for the product. The stability study test results further confirmed this inference.

**(ii) key physicochemical characteristics (e.g., water content, solubility, particle size distribution, polymorphic or solid state form) of the drug substance that can influence the performance of the drug product:**

Ambrosol HCl is an acid labile substance below pH 3. The milled material has minimal solubility in neutral and alkaline pH. However, the micronized material has significantly improved dissolution, and hence was chosen for use in the tablets (see details in 2.3.S.3.1). The preformulation study indicated that the drug substance is slightly photosensitive, and could lose potency when exposed to light for long duration. This has been addressed by coating the tablets with adequate opacifying agent. The stability study results indicate the chosen composition for the formulation is most suitable to ensure the required quality and performance.

The particle sizes for batches of drug substance used in the nonclinical, clinical, and stability lots are as follows:

| Parameter | Acceptance Criteria | Batch Number (and use) | | |
|---|---|---|---|---|
| | | G123 (nonclinical) | J456 (clinical and stability studies) | C789 (clinical and stability studies) |
| D (v, 0.1) | NLT 1.5 µm | 3.2 µm | 2.3 µm | 2.8 µm |
| D (v, 0.5) | 4.0 to 8.0 µm | 6.4 µm | 5.1 µm | 5.3 µm |
| D (v, 0.9) | NMT 20 µm | 17.0 µm | 14.5 µm | 15.1 µm |

**(iii) for combination products, compatibility of drug substances with each other:**

N/A (not a combination product).

### *2.3.P.2.1.2 Excipients (Ambrosia® Delayed-release Tablets, EC Tablets)*

**(a) Discussion of the choice of excipients listed in 2.3.P.1 (e.g., their concentrations, their characteristics that can influence the drug product performance):**

Below is a discussion of the choice of excipients:

| Excipient | Function | Discussion |
|---|---|---|
| ***Tablet Core*** | | |

| | | |
|---|---|---|
| Microcrystalline Cellulose, NF (Avicel PH-102) | filler/binder/ disintegrant | multi-functional, versatile excipient and is completely compatible |
| Povidone, USP (PVP-K 30) | binder/ disintegrant | a very good binder, disintegrant, soluble in water |
| Crospovidone, NF | disintegrant | super disintegrant, compatible |
| Magnesium Stearate, NF | lubricant | very good lubricant |
| Colloidal Silicon Dioxide, NF (Cab-O-Sil) | glidant | excellent glidant which may also improve disintegration, provides very good tablets at high compression speed |
| ***Coating*** | | |
| Methacrylic Acid Copolymer (Type C), NF | enteric coating agent | compatible, and a pH dependent anionic aqueous polymer dispersion solubilizing above pH 5.5. |
| Polyethylene Glycol, NF | plasticizer | makes film pliable and continuous |
| Triethyl Citrate, NF | plasticizer | makes film pliable and continuous |
| Talc, USP | opacifier | protects the drug substance from exposure to light |
| Titanium Dioxide, USP | opacifier | protects the drug substance from exposure to light |
| FD&C Red No. 4, House | colourant | approved colour according to Canadian Food and Drug Regs. |
| D&C Yellow No.10, House | colourant | approved colour according to Canadian Food and Drug Regs. |
| FD&C Blue No. 2, House | colourant | approved colour according to Canadian Food and Drug Regs. |
| ***Printing*** | | |
| Superwhite® Printing Ink, House | printing ink | has a long history of use in pharmaceuticals |

### *2.3.P.2.2 Drug Product (Ambrosia® Delayed-release Tablets, EC Tablets)*

#### *2.3.P.2.2.1 Formulation Development (Ambrosia® Delayed-release Tablets, EC Tablets)*

**(a) Summary describing the development of the drug product (e.g., route of administration, usage):**

All the excipients used in the tablet formulation are commonly used in the manufacture of solid oral dosage forms.

Pre-formulation work showed that Ambrosol is unstable in acid pH (below pH 3). However, the micronized drug is fairly soluble in water and alkaline buffer solutions. Published literature and preliminary PK studies demonstrate that Ambrosol is well absorbed in the ileum and jejunum. Hence, it was decided to formulate Ambrosol as a modified release tablet with an enteric coat.

Lactose was originally used as a diluent early in developmental studies. Also the earlier lots did not contain Crospovidone and Colloidal Silicon Dioxide. However, the tablets generated did not meet the expected specifications for tablets (content uniformity and dissolution). Replacing Lactose with Microcrystalline Cellulose as the filler and addition of Colloidal Silicon Dioxide improved tableting properties, and dissolution of the tablets.

Various formulations were made initially during the pharmaceutical

development, and the final formulation was chosen based on test results. The developmental work is summarised below (see Module 3.2.P.2.2.1, pages 205-245 for details).

| **Parameter** | **Formulation 1 (milled DS) (e.g., (L) A75-A1)** | **Formulation 2 (micronized DS) (e.g., (L) A75-B1)** | **Formulation 3 (micronized DS) (e.g., (L) A75-001)** | **Formulation 4 (micronized DS) (e.g., (L) A75-002)** |
|---|---|---|---|---|
| | ***In vitro* studies** | ***In vitro* studies** | **Pivotal clinical (75 mg tablets)** | **Bridging BE study (75 mg tablets)** |
| Composition | DS, Lactose, PVPK30, Mg St | DS, MCC, PVPK30, Mg St | DS, MCC, PVPK30, Mg St, CrosPVP | DS, MCC,PVPK30, Mg St, CrosPVP, silicon dioxide |
| Process | Direct compression | Wet granulation, LOD NMT 7% | Wet granulation, LOD NMT 5% | Wet granulation, LOD NMT 4.5% |
| Tableting | poor flow, Weight Variation | problem exists but improved flow, improved Weight Variation | problem exists but significantly improved flow, Weight Variation* | good flow<br>no Weight Variation problems |
| Dissolution, pH 6.8 | 80% in 120 min | 80% in 50 min | 80% in 30 min | 85% in 25 min |
| Coated tablets | | | | |
| Methacrylic acid copolymer (Type C) + other solids | 5% | 7% | 8% | 10% |
| Amount released in pH 1.2 in 2 hours | 15% | 9% | 4% | <2% |
| Amount released in pH 6.8 in 30 minutes | 40 % | 75% | 80% | 90% |

***** the cores were sorted using Mocon balance to ensure all cores were of acceptable weight and suitable for use in the clinical trial

**(b) Discussion of the differences in the formulations for the batches used the in the *in vivo* studies (e.g., pivotal clinical, comparative bioequivalence) and the formulation described in 2.3.P.1:**

The pivotal clinical trials were done using 75 mg tablets with Formulation 3. Subsequently, during pharmaceutical development it was realized the formulation needed 0.2% Colloidal Silicon Dioxide, in addition to drying the granules to a maximum of 4.5% moisture, to improve granule flow to manufacture tablet cores with consistent quality. Since the addition of Colloidal Silicon Dioxide was a qualitative change to the formulation (i.e., Formulation 4), a bridging *in vivo* bioequivalence study was conducted between Formulations 3 and 4 to support the change. The two formulations were found bioequivalent. The comparative dissolution tests were also acceptable.

**(c) Description of batches used in the comparative *in vitro* studies (e.g., dissolution) and in the *in vivo* studies (e.g., pivotal clinical, comparative bioequivalence), including strength, batch number, and type of study:**

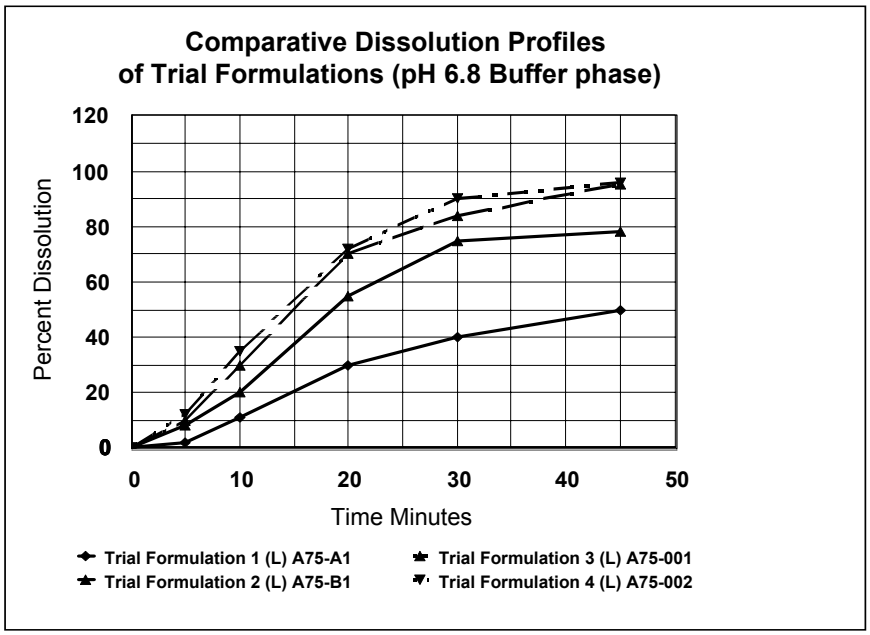
| Strength | Drug Product Batch No. | Formulation No. or Code | Type of Study (and Code No. if applicable) |
|---|---|---|---|
| 25 mg | A25-001 | Formulation 3 | *In vitro* dissolution |
| 50 mg | A50-001 | Formulation 3 | *In vitro* dissolution |
| 75 mg | A75-A1 | Formulation 1 | *In vitro* dissolution |
| 75 mg | A75-B1 | Formulation 2 | *In vitro* dissolution |
| 75 mg | A75-001 | Formulation 3 | Pivotal clinical study (randomized, placebo-controlled, double-blind (Drugs-R-075-1)), bridging *in vivo* bioequivalence (Drugs-R-075-2) and *in vitro* dissolution |
| 75 mg | A75-002 | Formulation 4 | Bridging *in vivo* bioequivalence (Drugs-R-075-2) and *in vitro* dissolution |

**(d) Summary of results for comparative *in vitro* studies (e.g., dissolution) and comparative *in vivo* studies (e.g., bioequivalence):**

*Summary of comparative in vitro dissolution studies:*

Please note the Similarity ($f_2$) factor values were used as an indicator in the comparative dissolution profiles, e.g., if they are in the low 40's or below to warrant further investigation; if the $f_2$'s are in 50's or above, similarity in drug release was assumed. All calculations were determined using n =12 and only one time point after reaching 80% were used in the calculation.

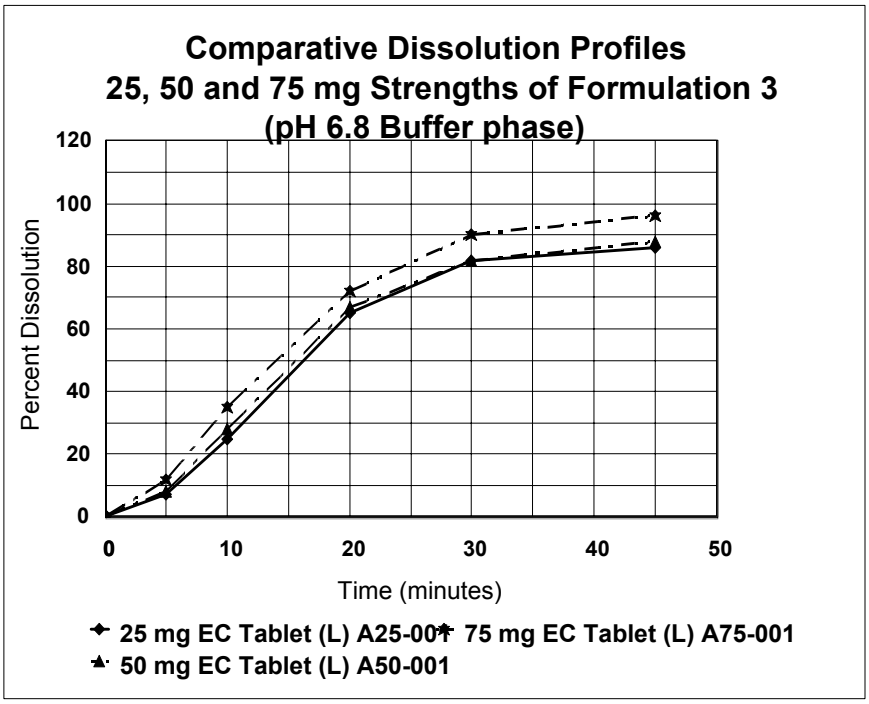
(1) Comparison of Formulations 1-4 (75 mg tablets):




| Time | Formulation 1 (L) A75-A1 | Formulation 2 (L) A75-B1 | Formulation 3 (L) A75-001 (ref - clinical) | Formulation 4 (L) A75-002 (bridging bioeq.) |
|---|---|---|---|---|
| 5 | 2 | 8 | 10 | 12 |
| 10 | 11 | 20 | 30 | 35 |
| 20 | 30 | 55 | 70 | 72 |
| 30 | 40 | 75 | 84 | 90 |
| 45 | 50 | 78 | 95 | 96 |
| $f_2$ | 25.01 | 43.57 | -- | 72.43 |

The above results indicate Formulation 1 and 2 do not meet the quality expectations. Formulation 3 was found acceptable and was used in pivotal clinical studies. Since Formulation 4 included a qualitative change to the formulation (i.e., addition of colloidal silicon dioxide), a bridging *in vivo* bioequivalence study was conducted. In addition, the Formulation 4 was manufactured at an alternate site from the site used to manufacture the clinical study batch. The similarity value ($f_2 = 72$) indicates Formulation 3 and Formulation 4 are similar. This is also supported by BE study discussed in Module 2.7.

(2) Comparison between 25 mg, 50 mg, and 75 mg tablets made with Formulation 3:




| Time | 25 mg (L) A25-001 | 50 mg (L) A50-001 | 75 mg (L) A75-001 (ref - clinical) |
|---|---|---|---|
| 5 | 7 | 8 | 12 |
| 10 | 25 | 28 | 35 |
| 20 | 65 | 67 | 72 |
| 30 | 82 | 82 | 90 |
| 45 | 86 | 88 | 96 |
| $f_2$ | 56.04 | 60.70 | -- |

The three strengths, 25 mg, 50 mg and 75 mg were carefully designed to ensure proportionality of ingredients (using a common granulation) and tooling to obtain tablets with proportional surface areas. The similarity factor ($f_2$) values greater than 50 indicate they all have similar release rates. The rates of release at earlier time points (10-30 minutes) are faster for the larger tablets, which is expected since they have larger surface areas and more net drug load.

*Summary of comparative in vivo bioequivalence studies:*

Results and Discussion:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA
Formulation 3versus Formulation 4
(a single 75 mg dose - 1 x 75 mg)
Oral administration of Ambrosol in the Fasting State

From Measured Data

| Parameter | Test** | Reference*** | % Ratio of Geometric Means | 90% Confidence Interval |
|---|---|---|---|---|
| $AUC_T$ (ng.h/mL) | 110.835<br>131.743 (62.8) | 98.690<br>121.128 (61.8) | 112.18 | 101.59 – 123.88 |
| $AUC_I$ (ng.h/mL) | 117.631<br>137.935 (64.3) | 106.500<br>130.989 (68.2) | 110.54 | 99.54 – 122.76 |
| $C_{MAX}$ (ng/mL) | 22.899<br>24.988 (49.2) | 22.063<br>25.946 (83.4) | 103.97 | 93.89 – 115.13 |
| $T_{MAX*}$ (h) | 3.09 (86.0) | 3.10 (102.6) | --- | --- |
| $T_{½}$ (h) | 5.34 (41.1) | 5.29 (73.0) | --- | --- |

* expressed as arithemetic mean (CV%) only
** Formulation 4: (L) A75-002
*** Formulation 3: (L) A75-001

The above results show that Formulations 3 and 4 are considered bioequivalent, thus the proposed commercial product (using Formulation 4) is equivalent to the product used in the pivotal clinical studies (using Formulation 3).

**(e) Summary of any information on *in vitro-in vivo* correlation (IVIVC) studies (with cross-reference to the studies in Module 5):**

N/A (an *IVIVC* study was not attempted).

**(f) For scored tablets, provide rationale/justification for scoring:**

N/A (tablets are not scored).

***2.3.P.2.2.2 Overages (Ambrosia® Delayed-release Tablets, EC Tablets)***

**(a) Justification of overages in the formulation(s) described in 2.3.P.1:**

No overages of drug substance or excipient were added in the core tablet. The master batch record has a 10% overage in the coating solution. This excess is required to fill the dead volumes in the coating tubes. Since, the coating process is monitored based on weight gain, the excess of costing solution is considered justified. The quality of the tablet is further ascertained by in-process and finished product testing.

***2.3.P.2.2.3 Physicochemical and Biological Properties (Ambrosia® Delayed-release Tablets, EC Tablets)***

**(a) Discussion of the parameters relevant to the performance of the drug product (e.g., pH, ionic strength, dissolution, particle size distribution, polymorphism, rheological properties):**

The enteric coating used in the formulation starts to disintegrate at approximately pH 4, therefore, there is minimal release (e.g., NMT 10.0%) in the pH range where the drug substance was observed to be labile (e.g., pH below 3).

A batch of drug product manufactured with drug substance having a particle size distribution D (v, 10) = 20 µm, D (v, 50) = 71 µm, D (v, 90) = 203 µm showed failed to meet the dissolution acceptance criteria. Drug product containing the micronized drug substance showed acceptable dissolution in pH above 4.5. As such, using micronized drug substance with the particle size acceptance criteria as proposed is considered warranted to produce drug product with acceptable dissolution quality standards.

***2.3.P.2.3 Manufacturing Process Development (Ambrosia® Delayed-release Tablets, EC Tablets)***

**(a) Discussion of the development of the manufacturing process of the drug product (e.g., optimization of the process, selection of the method of sterilization):**

See discussions under Module 2.3.P.2.2.1.

**(b) Discussion of the differences in the manufacturing process(es) for the batches used the in the *in vivo* studies (pivotal clinical, comparative bioequivalence) and the process described in 2.3.P.3.3:**

With the exception of batch size increase (i.e., 100,000 units for the clinical and bioequivalence batches versus 1,000,000 units for full scale production), the proposed commercial process is identical to the process for the batches used in the bridging *in vivo* bioequivalence study (Formulation 4).

The formulation differences between the process for the batches used in the pivotal clinical studies (Formulation 3) and the process for the batches used in the bioequivalence study (Formulation 4) has been previously described (see discussions under Module 2.3.P.2.2.1). These differences have been shown not to have an impact on the safety and efficacy of the product as the products in the bridging study were shown to be bioequivalent.

In addition to demonstrating the qualitative formulation change has not affected the safety and efficacy of the product, the bridging *in vivo* bioequivalence study has also demonstrated that the change in manufacturing site has not affected the safety and efficacy of the product. The batch used in the pivotal clinical trials ((L) A75-001) was manufactured at "City 4, Country D". The batch used in the bridging *in vivo* bioequivalence study ((L) A75-002) was manufactured at "City 5, Country E". The results of the bioequivalence study confirm that product manufactured from both sites are considered bioequivalent. In addition, the comparative dissolution profiles of A75-001 and A75-002 had a similarity factor ($f_2$) = 72 further supporting that Formulation 3 and Formulation 4 are considered similar.

Batches using the proposed full scale commercial process (Formulation 5) have yet to be manufactured, but will be manufactured and included in the process validation studies (see Module 2.3.P.3.5 for a summary of the proposed process validation studies).

***2.3.P.2.4 Container Closure System (Ambrosia® Delayed-release Tablets, EC Tablets)***

**(a) Discussion of the suitability of the container closure system (described in 2.3.P.7) used for the storage, transportation (shipping), and use of the drug product (e.g., choice of materials, protection from moisture and light, compatibility of the materials with the dosage form):**

The tablets to be marketed in Canada will be manufactured in City 4, Country D. A simulated transportation study was performed to mimic the transit temperature and humidity conditions. The details are given in Module 3.2.P.2.4, pages 78-85. The results were satisfactory, and there were no unusual observations. In addition, the three process validation batches will be tested in Canada to complete the validation.

The stability studies under long term (12 months at 25ºC/60% RH) and accelerated (6 months at 40ºC / 75% RH) conditions further support the choice of packaging, and short term exposure to higher temperature and humidity conditions (Module 3.2.8.3, pages 11-35). There were not any compatibility issues observed with the proposed container closure systems.

***2.3.P.2.5 Microbiological Attributes (Ambrosia® Delayed-release Tablets, EC Tablets)***

**(a) Discussion of microbiological attributes of the dosage form (e.g., preservative effectiveness studies):**

N/A (the proposed product is a solid oral, non-sterile product).

***2.3.P.2.6 Compatibility (Ambrosia® Delayed-release Tablets, EC Tablets)***

**(a) Discussion of the compatibility of the drug product (e.g., with reconstitution diluent(s) or dosage devices, co-administered drugs):**

N/A (the proposed product is a solid oral dosage form).

## 2.3.P.3 Manufacture (Ambrosia® Delayed-release Tablets, EC Tablets)

### *2.3.P.3.1 Manufacturer(s) (Ambrosia® Delayed-release Tablets, EC Tablets)*

**(a) Name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing:**

| Name and Address | Responsibility | Drug Master File Number |
|---|---|---|
| Testy Inc.<br>789 High Road<br>City 3, Country C | testing of the drug substance<br>(particle size testing only) | N/A |
| Drugs 'R' Us<br>111 First Avenue<br>City 4, Country D | manufacturing, packaging, labelling, testing, storage, distribution<br>(for drug product intended for the North American market) | N/A |
| Drugs 'R' Us<br>111 My Street<br>City 5, Country E | manufacturing, packaging, labelling, testing, storage, distribution<br>(for drug product intended for the European market) | N/A |
| Drugs 'R' Us<br>111 Medicine Crescent<br>City 6, Canada | storage and distribution<br>(for Canadian market) | N/A |

**(b) List of referenced Drug Master Files (DMFs) and DMF Numbers (copies of DMF letters of access should be located in Module 1):**

N/A (there are not any cross-referenced DMFs for the production of the drug product).

**(c) Confirmation that all facilities involved in the production have a Good Manufacturing Practices (GMP) compliance rating and/or an Establishment License (EL) (GMP and/or EL information should be located in Module 1):**

The above manufacturing facilities have a valid Establishment License (EL) to manufacture the proposed dosage form (i.e., tablets). In addition, the contract testing facility also has a valid Establishment License.

Copies of the EL information can be found in Module 1.2.5, pages 2-4.

### *2.3.P.3.2 Batch Formula (Ambrosia® Delayed-release Tablets, EC Tablets)*

**(a) List of all components of the dosage form to be used in the manufacturing process, and their amounts on a per batch basis (including overages, if any):**

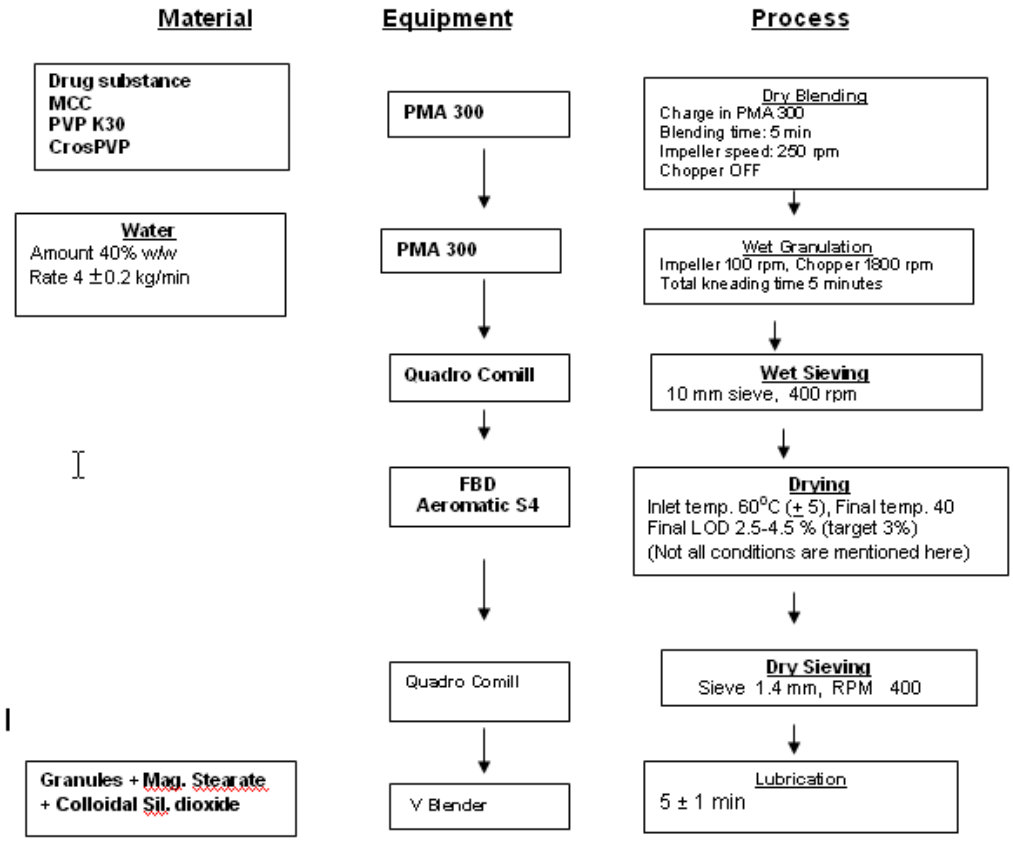
| **Strength (label claim as base)** | | **25 mg (base)** | **50 mg (base)** | **75 mg (base)** |
|---|---|---|---|---|
| **Master Production Document Reference Number and/or Version** | | **Formulation 5 (MBR-001, ver. 1.0)** | **Formulation 5 (MBR-002, ver. 1.0)** | **Formulation 5 (MBR-003, ver. 1.0)** |
| **Batch Size(s) (number of dosage units)** | | **1,000,000** | **1,000,000** | **1,000,000** |
| **Component and Quality Standard (and Grade, if applicable)** | **Function** | **Quantity per batch** | **Quantity per batch** | **Quantity per batch** |
| ***Tablet Core*** | | | | |
| Ambrosol HCl, Professed[a] | active[a] | 30.0 kg | 60.0 kg | 90.0 kg |
| Microcrystalline Cellulose, NF (Avicel PH-102) | filler/binder/ disintegrant | 55.0 kg | 110.0 kg | 165.0 kg |
| Povidone, USP (PVP-K 30) | binder/ disintegrant | 9.0 kg | 18.0 kg | 27.0 kg |
| Crospovidone, NF | disintegrant | 5.0 kg | 10.0 kg | 15.0 kg |
| Magnesium Stearate, NF | lubricant | 0.8 kg | 1.6 kg | 2.4 kg |
| Purified Water, USP[b] | granulat. fluid | (40.0 kg) | (80.0 kg) | (120.0 kg) |
| Colloidal Silicon Dioxide, NF (Cab-O-Sil) | glidant | 0.2 kg | 0.4 kg | 0.6 kg |
| ***Coating (10% weight gain)***[c] | | | | |
| Methacrylic Acid Copolymer (Type C), NF | enteric coating agent | 7.7 kg | 15.4 kg | 23.1 kg |
| Polyethylene Glycol, NF | plasticizer | 0.55 kg | 1.1 kg | 1.65 kg |
| Triethyl Citrate, NF | plasticizer | 0.55 kg | 1.1 kg | 1.65 kg |
| Talc, USP | opacifier | 0.55 kg | 1.1 kg | 1.65 kg |
| Titanium Dioxide, USP | opacifier | 0.55 kg | 1.1 kg | 1.65 kg |
| FD&C Red No. 4, House | colourant | 1.1 kg | -- | -- |
| D&C Yellow No.10, House | colourant | -- | 2.2 kg | -- |
| FD&C Blue No. 2, House | colourant | -- | -- | 4.5 kg |
| Purified Water, USP[b] | solvent | qs to 25.0 kg | qs to 50.0 kg | qs to 75.0 kg |
| ***Printing*** | | | | |
| Superwhite® Printing Ink, House | printing ink | trace | trace | trace |
| ***Total (excluding water)***[b] | | 110.0 kg | 220.0 kg | 330.0 kg |

[a] Each tablet contains 1.0 mg of Ambrosol (active base) per 1.2 mg of Ambrosol HCl (salt).
[b] Purified Water is removed during the manufacturing process.
[c] The coating solution has 10% excess to material to fill the voids in the tubes etc.

Typical granulation lot size is 100 kg (the size of 25 mg lot). The batch for the 50 mg strength is made by mixing two sublots of 100 kg, and the batch for the 75 mg strength is made by mixing three sublots of 100 kg. The coating operations for the 25 mg, 50 mg, and 75 mg strengths are done in a lot sizes of 25 kg, 50 kg, and 75 kg, respectively.

*2.3.P.3.3 Description of Manufacturing Process and Process Controls (Ambrosia® Delayed-release Tablets, EC Tablets)*

**(a) Flow diagram of the manufacturing process:**




**Compression: Manesty Betapress**
**Weight Variation:** Individual ± 4%, Average ± 2%, **Disintegration Time:** 10 min,
**Friability:** NMT 1%, **Hardness:** 25 mg: 5-8 kp; 50 mg: 7-10 kp; 75 mg: 8-12 kp.

**Enteric coating: O'Hara Labcoat II**
**Pan speed:** 14 ± 3, **Spray rate:** 15 ± 5 g/min,
**Temperature:** Supply 70 ±5°C, **Exhaust** 43 ±5°C, **Weight gain**: 10 ±1%
**Each load is about 100 kg**
**Only critical operational conditions are mentioned above.**

Typical granulation lot size is 100 kg (the size of 25 mg lot). The batch for the 50 mg strength is made by mixing two sublots of 100 kg, and the batch for the 75 mg strength is made by mixing three sublots of 100 kg. The coating operations for the 25 mg, 50 mg, and 75 mg strengths are done in a lot sizes of 25 kg, 50 kg, and 75 kg, respectively.

**(b) Narrative description of the manufacturing process, including equipment type and working capacity, process parameters:**

**Granulation:**

The granulation is made by aqueous wet granulation process using a high shear mixing granulator. The drug substance, MCC, PVP K30 and Crospovidone are charged in a Fielder, PMA 300 and mixed for 5 ± 1 minutes at 250 rpm. Then 40% by weight of purified water is sprayed while setting the granulator impeller to 100 rpm and chopper to 1800 rpm. The total kneading time including the spraying time is kept below 6 minutes. The wet granules are broken down using a Quadro Comil with 10 mm sieve set at 400 rpm. The granules are charged in a Aeromatic S4 fluid bed drier, and dried, setting the inlet temperature to 60ºC. The drying is performed until a Loss on Drying (LOD) of 2.5-4.5% is reached. The dried granules are milled using a Quadro Comil with 1.4 mm sieve, set to 400 rpm. The milled granules are charged in a 20 cu. ft. V blender and lubricated with magnesium stearate and colloidal silicon dioxide for 5 ± 1 minutes.

**Compression:**

The cores are compressed using Betapress. The parameters are as follows:

Weight Variation: individual ± 4%, average ± 2%,
Disintegration Time (without disk): 10 min,
Friability: NMT 1%
Hardness: 5-8 kp (25 mg), 7-10 kp (50 mg), 8-12 kp (75 mg)

**Coating:**

The compressed cores are enteric coated using a O'Hara 30" perforated pan. The pan speed is kept at 14 ± 3, No. of guns: 2, Spray rate: 15 ± 5 g/min, Temperature: supply 43 ± 5ºC, Exhaust: 43 ± 5ºC. The cores are coated to a target limit of 10 ± 1 % weight gain.

**Packaging:**

The coated tablets are packed in blisters or HDPE bottles. The blister packaging operation is tested periodically (every 30 minutes) for 'leak test'. The HDPE bottles are checked periodically (every 30 minutes) for integrity of thermosealing.

**(c) Justification of reprocessing of materials:**

N/A (no reprocessing procedure has been proposed).

***2.3.P.3.4 Controls of Critical Steps and Intermediates (Ambrosia® Delayed-release Tablets, EC Tablets)***

**(a) Summary of controls performed at the critical steps of the manufacturing process and on isolated intermediates:**

All the important steps in the processing were identified after making a series of small scale lots (1- 10 kg size). Then, using factorial design the critical steps were identified, which are as follows:

**Granulation:**

Dry mixing: mixing speed and time
Massing: Rate of addition of water, quantity of water, impeller speed (chopper speed was not critical)
Wet milling: was not critical
Dry milling: Sieve size and rpm
Lubrication: mixing time and speed

**Compression:**

Weight and hardness

**Coating:**

% solids, spray rate, pan speed, tablet weight gain

The above critical conditions were first optimised for a medium size lot (50 kg scale-up lot), and then finally for the commercial size lots (100 kg). The process parameters and their range are described in the flow chart. The 50 mg lots are made as two sublots of 100 kg each and the 75 mg lots are made as three sublots of 100 kg each. The validation protocol includes these critical parameters.

***2.3.P.3.5 Process Validation and/or Evaluation (Ambrosia® Delayed-release Tablets, EC Tablets)***

**(a) Summary of the process validation and/or evaluation studies conducted or a summary of the proposed validation protocol for the critical steps or critical assays used in the manufacturing process (e.g., protocol number, parameters, results):**

The first three consecutive commercial size batches for Ambrosol Hydrochloride Delayed Release tablets 25 mg, 50 mg and 75 mg will be validated according to *Process Validation Protocol No. PVP-001, ver. 1.0*.

Three proportional strengths of Ambrosia Delayed Release Tablets are produced but the batch sizes are different between strengths. The batch sizes are 100 kg, 200 kg and 300 kg respectively, therefore the manufacturing process will be validated for each strength where necessary (lubrication, compression, and coating will be done for each strength separately). Since the granulation process (up to drying and milling) is common to all strengths and is done in sublots of 100 kg, three granulation lots (100 kg each) will be validated.

In addition, the increase in batch size (from 100,000 units to 1,000,000 units) will be validated as part of the studies.

Master batch formulas (25 mg: No. MBR-001, ver. 1.0; 50 mg MBR-002, ver. 1.0; and 75 mg MBR-003) have been prepared and all information about the manufacturing process has been included.

The IQ/OQ files for the major equipment used to manufacture Ambrosol tablets 25 mg, 50 mg and 75 mg will be checked for compliance, prior to the process validation performance.

***Granulation:***

Process Validation will consist of the following parameters and additional validation will be conducted for each strength where warranted due to differences in batch size.

a) Process validation of the dry mixing step which is the blending of ambrosol hydrochloride, microcrystalline cellulose, povidone and crospovidone, will consist of validating the Fielder - PMA 300 high shear mixer at the targeted speed and time. To demonstrate blend uniformity, 6 samples will be taken from predetermined positions of the mixer using a sampling thief.

b) Process validation of the wet granulation step which is the granulating of the dry mix with water, will consist of the feed rate of water, impeller speed, chopper speed and kneading time.

c) Process validation of the drying of the wet granules will be validated by verifying the operating parameters of the Aeromatic S4 fluid bed dryer through the monitoring to the target inlet and outlet temperatures and by monitoring moisture until the target value is reached.

d) Process validation of the milling of dry granules will consist of verifying the targeted speed of the Quadro Comil with a 1.4 mm sieve

e) Process validation of the final blending of the dried granules with magnesium stearate will consist of verify the mixing speed and time of the V-blender. This step will be validated for each strength as the size of the V-Blender is dependent on the size of the batch. To demonstrate blend uniformity, 10 samples will be taken from predetermined positions of the mixer using a sampling thief.

***Compression:***

Process Validation of the Betapress will consist of the following parameters for each strength.

a) For minimum, median (target) and maximum speed limits: A minimum of 5 kg granules will be subjected to minimum, median, and maximum speed (total of 15 kg).

b) The tablets collected at each condition will be tested for weight variation (individual tablets ± 4% and for average of 10 tablets is ± 2%), disintegration

(NMT 10 minutes), friability (NMT 1%), and hardness (limits given below).

At the target compression speed a minimum of 5 kg granules will be subjected to minimum, target and maximum hardness. The hardness limits are as follows:

25 mg: 5 - 8 kp;
50 mg: 7 - 10 kp;
75 mg: 8 - 12 kp

The tablets collected at each condition will be tested for weight variation, disintegration (NMT 10 minutes), and friability (NMT 1%).

***Film Coating Process:***

Process validation of the O'Hara Labcoat II will consist of the following parameters for each strength.

a) Validation of the pan speed at the targeted value.

b) Validation of the spray rate at the targeted value.

c) Validation of the supply temperature at the targeted value.

d) Validation of the exhaust temperature at the targeted value.

e) Collection of 250 coated tablets from each of the front, middle and back of the coating pan to measure weight gain and efficiency of the process. Secondly, drug release testing in both phases will be conducted to ensure uniform application of the enteric coating process.

The process validation batches will cover both proposed manufacturing sites. Comparative profiles from drug release testing will be prepared on samples from each of the manufacturing sites compared to the profile of the pivotal clinical batch. The acceptance criteria for the comparison would be a similarity factor ($f_2$) of between 50 and 100. $f_2$ values below 50 would warrant further investigation.

## 2.3.P.4 Control of Excipients (Ambrosia® Delayed-release Tablets, EC Tablets)

### *2.3.P.4.1 Specifications (Ambrosia® Delayed-release Tablets, EC Tablets)*

**(a) Summary of the specifications for non-compendial excipients and for compendial excipients which include supplementary tests not included in the monograph(s):**

Copies of the specifications for the following non-compendial excipients can be found in Module 3.2.P.4.1, pages 10-15:

- FD&C Red No. 4, House
- D&C Yellow No. 10, House

- FD&C Blue No. 2, House
- Superwhite® Printing Ink, House

Copies of test results for one lot of each of the non-compendial excipients are included in Module 3.2.P.4.1, pages 25-35.

**(b) Confirmation that none of the excipients which appear in the drug product are prohibited for use in drugs by the Canadian *Food and Drug Regulations*:**

None of the excipients which appear in the drug product are prohibited for use in drugs by the Canadian *Food and Drug Regulations*.

The colouring agents used in the formulations are permitted in drugs for internal and external use according to Section C.01.040.2 (3) of the *Food and Drug Regulations*.

**(c) List of referenced Drug Master Files (DMFs) and DMF Numbers (copies of DMF letters of access should be located in Module 1):**

| Name and Address | Material | Drug Master File Number |
|---|---|---|
| Colourbuster Inc.<br>333 Holland Avenue<br>City 5, Country E | Superwhite® Ink, House | DMF 2005-5678 |

It has been confirmed that DMF 2005-5678 has been received by Health Canada and that the necessary Cost Recovery Fees have been paid by the DMF Holder Colourbuster Inc.

A copy of the Letter of Access for DMF 2005-5678 allowing access of Health Canada for this submission can be found in Module 1.2.6.

***2.3.P.4.2 Analytical Procedures (Ambrosia® Delayed-release Tablets, EC Tablets)***

**(a) Summary of the non-compendial analytical procedures:**

N/A (only compendial analytical procedures are used).

***2.3.P.4.3 Validation of Analytical Procedures (Ambrosia® Delayed-release Tablets, EC Tablets)***

**(a) Summary of the validation information for the non-compendial analytical procedures:**

N/A (only compendial analytical procedures are used).

***2.3.P.4.4 Justification of Specifications (Ambrosia® Delayed-release Tablets, EC Tablets)***

**(a) Justification of the specifications (e.g., evolution of tests, analytical procedures, and acceptance criteria, exclusion of certain tests, differences from compendial standard):**

The specifications for the non-compendial excipients are based on information provided by the respective suppliers. Each of these specifications include a suitable, specific test for Identification.

### *2.3.P.4.5 Excipients of Human or Animal Origin (Ambrosia® Delayed-release Tablets, EC Tablets)*

**(a) List of excipients that are of human or animal origin (including country of origin):**

N/A (all excipients, including the magnesium stearate, are obtained from non-animal sources).

**(b) Summary of the information (e.g., sources, specifications, description of the testing performed, viral safety data) regarding adventitious agents for excipients of human or animal origin:**

N/A (all excipients, including the magnesium stearate, are obtained from non-animal sources).

**(c) For excipients obtained from sources that are at risk of transmitting Bovine Spongiform Encephalopathy (BSE)/Transmissible Spongiform Encephalopathy (TSE) agents (e.g., ruminant origin), a letter of attestation (with supporting documentation) should be provided confirming that the material is not from a BSE/TSE affected country/area. A copy of the letter may be found in:**

N/A (all excipients, including the magnesium stearate, are obtained from non-animal sources).

### *2.3.P.4.6 Novel Excipients (Ambrosia® Delayed-release Tablets, EC Tablets)*

**(a) Summary of the details on the manufacture, characterization, and controls, with cross references to supporting safety data (nonclinical and/or clinical) on novel excipients (i.e., those used for the first time in a drug product or by a new route of administration):**

N/A (all of the excipients are not considered "novel" as they are commonly used for the type of dosage form).

## 2.3.P.5 Control of Drug Product (Ambrosia® Delayed-release Tablets, EC Tablets)

### *2.3.P.5.1 Specification(s) (Ambrosia® Delayed-release Tablets, EC Tablets)*

**(a) Specification(s) for the drug product:**

| **Standard Claimed (e.g., Professed, House, USP, BP)** | | Professed |
|---|---|---|
| **Specification Reference Number and/or Version** | | TS-DP-004 (April 1, 2004) |
| **Test** | **Acceptance Criteria (release and stability)** | **Analytical Procedure (Type/Source/Version)** |
| Description[a,b] | 25 mg: red, round, biconvex, enteric coated tablet imprinted with "Happy-day" on one side and "25 mg" on the other | Visual/House/TM-DP-01, ver. 1.0 |
| | 50 mg: yellow, round, biconvex, enteric coated tablet imprinted with "Happier-day" on one side and "50 mg" on the other | |
| | 75 mg: blue, round, biconvex, enteric coated tablet imprinted with "Happiest-day" on one side and "75 mg" on the other | |
| Identification[a] | A: IR conforms to standard<br>B: HPLC acive peak conforms to standard | A: IR/House/TM-DP-02, ver. 1.0<br>B: HPLC/House/TM-DS/DP-03, ver. 1.1 |
| Average Mass (of 10 tablets)[c] | 25 mg: 110 mg ± 3%<br>50 mg: 220 mg ± 3%<br>75 mg: 330 mg ± 3% | Gravimetry/House/TM-DP-04, ver. 1.0 |
| Moisture[a,b] | NMT 4.5% | LOD/House/TM-DP-07, ver. 1.0 |
| Uniformity of Dosage Units (Content Uniformity)[a] | meets USP requirements | HPLC/House/TM-DS/DP-03, ver. 1.1 |
| Assay (ambrosol (base) per tablet)[a,b] | Release: 95.0% to 105.0% of label claim<br>Shelf-life: 90.0% to 110.0% of label claim | HPLC/House/TM-DS/DP-03, ver. 1.1 |
| Drug Release[a,b]<br>(Apparatus 1, 50 rpm, 1L)<br>0.1N HCl Acid stage (pH 1.2)<br>Phosphate buffer stage (pH 6.8) | <br><br>NMT 10% in 2 hours<br>NLT 75% (Q) in 30 minutes | UV/House/TM-DP-06, ver. 1.0 |
| Degradation Products[b] | RC2: NMT 0.5%<br>Individual unspecified: NMT 0.2%<br>Total: NMT 1.0% | HPLC/House/TM-DS/DP-05, ver. 2.0 |

[a] = tested on release
[b] = tested on stability
[c] = tested in-process

A copy of the signed and dated specification TS-DP-004 (April 1, 2004) can be found in Module 3.2.P.5.1, pages 2-8.

### *2.3.P.5.2 Analytical Procedures (Ambrosia® Delayed-release Tablets, EC Tablets)*

**(a) Summary of the analytical procedures (e.g., key method parameters, conditions, system suitability testing):**

Due to the length of information, summaries of the following House analytical methods are attached to this Quality Overall Summary:

| Attachment | Summary | Analytical Procedure |
|---|---|---|

| | | |
|---|---|---|
| 1 | method | Assay: HPLC/House/TM-DS/DP-03, ver. 1.1 |
| 3 | method | Related Substances: HPLC/House/TM-DS/DP-05, ver. 2.0 |
| 9 | method | Drug Release: UV/House/TM-DP-06, ver. 1.0 |

***2.3.P.5.3 Validation of Analytical Procedures (Ambrosol Hydrochloride, Drugmaker Ltd.)***

**(a) Summary of the validation information (e.g., validation parameters and results):**

Due to the length of information, summaries of the validation reports for the following House analytical methods are attached to this Quality Overall Summary:

| Attachment | Summary | Analytical Procedure |
|---|---|---|
| 2 | validation report | Assay: HPLC/House/TM-DS/DP-03, ver. 1.1 |
| 4 | validation report | Related Substances: HPLC/House/TM-DS/DP-05, ver. 2.0 |
| 10 | validation report | Drug Release: UV/House/TM-DP-06, ver. 1.0 |

***2.3.P.5.4 Batch Analyses (Ambrosia® Delayed-release Tablets, EC Tablets)***

**(a) Description of the batches:**

| Strength and Batch Number | Batch Size | Date and Site of Production | Use (e.g., nonclinical, clinical, comparative) |
|---|---|---|---|
| 25 mg / A25-001 | 100,000 | mnfd.: 2004/06/01<br>pkgd.: 2004/06/30<br>site: City 4, Country D<br>(site for European market) | *In vitro* dissolution and stability |
| 50 mg / A50-001 | 100,000 | mnfd.: 2004/06/01<br>pkgd.: 2004/06/30<br>site: City 4, Country D<br>(site for European market) | *In vitro* dissolution and stability |
| 75 mg / A75-001 | 100,000 | mnfd.: 2004/06/01<br>pkgd.: 2004/06/30<br>site: City 4, Country D<br>(site for European market) | Pivotal clinical study (Drugs-R-075-1), bridging *in vivo* bioequivalence (Drugs-R-075-2), *in vitro* dissolution, and stability |
| 75 mg / A75-002 | 100,000 | mnfd.: 2005/01/15<br>pkgd.: 2005/01/30<br>site: City 5, Country E<br>(site for N. American market) | Bridging *in vivo* bioequivalence (Drugs-R-075-2), *in vitro* dissolution, and stability |

**(b) Summary of results for relevant batches (e.g., nonclinical, clinical, comparative):**

| Test | Acceptance Criteria | Results | | | |
|---|---|---|---|---|---|
| | | **25 mg / A25-001 (diss, stab)** | **50 mg / A50-001 (diss, stab)** | **75 mg / A75-001 (clin, bioeq, diss, stab)** | **75 mg / A75-002 (bioeq, diss, stab)** |
| Description[a,b] | see Module 2.3.P.5.1 | | | | |
| Identification[a] | A: IR conforms<br>B: HPLC conforms | | | | |
| Average Mass (of 10 tablets)[c] | 25 mg: 110 mg ± 3%<br>50 mg: 220 mg ± 3%<br>75 mg: 330 mg ± 3% | | | | |
| Moisture[a,b] | NMT 4.5% | | | | |
| Uniformity of Dosage Units (Content Uniformity)[a] | meets USP requirements | | | | |
| Assay (ambrosol (base) per tablet)[a,b] | Release: 95.0% to 105.0% of LC | | | | |
| Drug Release[a,b] (App. 1, 50 rpm, 1L)<br>Acid stage (pH 1.2)<br>Buffer stage (pH 6.8) | <br><br>NMT 10% in 2 hours<br>NLT 75% (Q) in 30 minutes | | | | |
| Degradation Products[b] | RC2: NMT 0.5%<br>Ind. unsp.: NMT 0.2%<br>Total: NMT 1.0% | | | | |

a = tested on release
b = tested on stability
c = tested in-process

Copies of the certificates of analyses for the above lots can be found in Module 3.2.P.5.4, page 2-20.

**(c) Summary of analytical procedures and validation information for those procedures not previously summarized in 2.3.P.5.2 and 2.3.P.5.3 (e.g., historical analytical procedures):**

N/A (all analytical procedures and validation information have been previously summarized in 2.3.P.5.2 and 2.3.P.5.3).

***2.3.P.5.5 Characterisation of Impurities (Ambrosia® Delayed-release Tablets, EC Tablets)***

**(a) Information on the characterization of impurities, not previously provided in 2.3.S.3.2 (e.g., summary of actual and potential degradation products, basis for setting the acceptance criteria):**

*Basis for Setting Acceptance Criteria:*

The various ICH Thresholds for this drug product are as follows:

| **Maximum Daily Dose:** | **75 mg** | |
|---|---|---|
| **Test** | **Parameter** | **ICH Threshold** |
| Related impurities (ref. ICH Q3B(R)) | Reporting Threshold | 0.1% |
| | Identification Threshold | 0.2% |
| | Qualification Threshold | 0.5% |

The maximum observed results in relevant batches are summarized as follows:

| **Impurity (drug-related and process-related)** | **Acceptance Criteria** | **Maximum Observed Results (include batch number and use) (e.g., nonclinical, clinical, comparative)** | | | |
|---|---|---|---|---|---|
| | | **25 mg / A25-001 (diss. and stab. studies)** | **50 mg / A50-001 (diss. and stab. studies)** | **75 mg / A75-001 (clin. bioeq., diss. and stab. studies)** | **75 mg / A75-002 (bioeq., diss., and stab. studies)** |
| RC1 | (not routinely tested in DP) | 0.11% | 0.12% | 0.07% | 0.07% |
| RC2 | NMT 0.5% | 0.3% | 0.2% | 0.4% | 0.3% |
| Maximum individual unspecified degradation product | NMT 0.2% | 0.15% (RRT = 4.2 min.) | 0.14% (RRT = 4.2 min.) | 0.13% (RRT = 4.2 min.) | 0.12% (RRT = 4.2 min.) |
| Total degradation products | NMT 1.0% | 0.6% | 0.4% | 0.7% | 0.6% |

RRT = relative retention time

As the concentration of Impurity RC1 did not increase under the various stress stability study, RC1 has been determined to be only a synthetic impurity and not a potential degradation product. As such, RC1 is not tested as part of the drug products specifications.

The concentration of Impurity RC2 did increase under stress conditions when the active ingredient was exposed to light and acid conditions. Furthermore, RC2 has been confirmed to be a potential degradation as its concentration also increased under accelerated (40ºC / 75% RH) and long term (25ºC / 60% RH) stability studies with time. As such, routine testing for RC2 as part of the drug product specifications is considered warranted.

In summary, the new drug product specification includes the following controls for impurities:

*Organic Impurities*

- a limit for the “specified identified degradation product” RC2 with an acceptance

criterion of NMT 0.5% corresponding to the ICH Qualification Threshold; since the proposed limit corresponds to the ICH Qualification Threshold, additional qualification is not considered necessary; furthermore, the results observed from the batch analyses (approx. 0.4%) support the proposed limit;

- a limit for "any unspecified degrdation product" with an acceptance criterion of NMT 0.2% corresponding to the ICH Identification Threshold;
- a limit of NMT 1.0% for "Total Degradation Product" based on the results observed from the batch analyses (approx. 0.7%).

*Residual Solvents*

- since organic solvents were not used in the manufacturing process for the drug product, testing for Residual Solvents is not warranted.

### *2.3.P.5.6 Justification of Specification(s) (Ambrosia® Delayed-release Tablets, EC Tablets)*

**(a) Justification of the drug product specification(s) (e.g., evolution of tests, analytical procedures, and acceptance criteria, differences from compendial standard):**

The ICH Q6A guideline has been consulted for the development of the drug product specification. The standard "Universal Tests" (i.e., Description, Identification, Assay, and Impurities) have been included.

The justification for the proposed acceptance criteria for the Impurities tests (Degradation Product and Residual Solvents) has been previously discussed (see Module 2.3.P.5.5).

Additional "Specific Tests" have been included which are common to this type of drug product, e.g.,:

*Uniformity of Dosage Units:* Testing by Content Uniformity has been adopted as the typical test for this parameter for this type of dosage form (e.g., coated tablets).

*Drug Release:* The dissolution method was developed primarily to satisfy the requirements of enteric coating, i.e., NMT 10% release in pH 1.2 in 2 hours, and almost complete release at pH 6.8 within 30 minutes. The method development was more focussed on the second part, i.e., pH 6.8. After screening a number of conditions the following conditions were finally chosen: Type II (paddle) set to 50 rpm, 1000 mL of phosphate buffer (0.05M sodium dihydrogen phosphate adjusted to pH 6.8 with NaOH), 37ºC. The method was found to have a certain degree of discriminatory quality (see graph differentiating the Formulations 1-4). To further establish the discriminatory quality of the method, two lots that differed in tablet hardness (75 mg tablet 8 kp versus 16 kp) were tested. The results (Module 3.2.P.4.1, pages 125-130) indicated the method was able to discriminate two lots that had similar composition but different hardness. No attempt was made to establish an in vitro/in vivo correlation. The same apparatus conditions were also suitable for the test in acid medium (0.1 N hydrochloric acid).

These tests are believed to suitably control the quality of the drug product.

### 2.3.P.6 Reference Standards or Materials (Ambrosia® Delayed-release Tablets, EC Tablets)

See discussions in Module 2.3.S.5 for information on in-house reference standard Batch Number GJC-2004-01. There are not any additional reference standards used for the drug product.

### 2.3.P.7 Container Closure System (Ambrosia® Delayed-release Tablets, EC Tablets)

**(a) Description of the container closure systems, including unit count or fill size, container size or volume:**

| Strength | Unit Count or Fill Size | Container Size(s) | Description |
|---|---|---|---|
| 25 mg | bottles of 100's | 75 mL bottle / 38 mm cap | *Container:* White, round, opaque, high density polyethylene (HDPE) bottles<br>*Closure:* White, round, opaque, polypropylene (PP) cap with EVA coated aluminum induction sealed liners and easy pull tabs |
| 50 mg | bottles of 100's | 125 mL / 44 mm cap | |
| 75 mg | bottles of 100's | 200 mL / 46 mm cap | |
| 25 mg, 50 mg, and 75 mg | 50's | 5 strips of 10 units per strip | *Unit dose blister:* 190 micron thick polyvinyl chloride (PVC) film and 7.5 mil aluminum foil coated with a heat seal laquer |

**(b) Materials of construction of each primary packaging component:**

| Packaging Component | Materials of Construction |
|---|---|
| bottles | HDPE |
| cap | PP cap, EVA coated aluminum liner |
| unit dose blisters | PVC, aluminum |

**(c) Summary of specifications of each primary and functional secondary (e.g., foil pouches) packaging components:**

| Packaging Component | Specification |
|---|---|
| bottle | description, dimensional conformance, volume, thermal analysis, multple internal reflectance, plastic identification (IR), light transmission, and water vapor permeation |
| cap | description, dimensional conformance, cap/bottle fit, average weight, cap identification (IR), liner identification (IR) |
| PVC blister | appearance, thickness of PVC film, identification (IR), moisture permeability |
| Aluminum foil backing | appearance, identification (IR) for laquer coating, thickness |

Copies of the specifications for the above container closure components can be found in Module 3.2.P.7, pages 15-30.

**(d) List of referenced Drug Master Files (DMFs) and DMF Numbers (copies of DMF letters of access should be located in Module 1):**

N/A (there are not any DMFs cross-referenced for information relating to the packaging components).

## 2.3.P.8 Stability (Ambrosia® Delayed-release Tablets, EC Tablets)

### *2.3.P.8.1 Stability Summary and Conclusions (Ambrosia® Delayed-release Tablets, EC Tablets)*

**(a) Summary of stress testing and results (e.g., photostability studies, cyclic studies for semi-solids, freeze-thaw studies):**

Refer to 2.3.S.7.1 for summaries of discussions of stress studies performed on the drug substance.

As the drug substance stress studies indicated the material is susceptible when exposed to light, photostability studies were conducted on the drug product. These studies were conducted in accordance with ICH's Q1B Photostability guideline.

The photostability study was conducted on one batch each for the three strengths under conditions compliant with ICH guideline. The test parameters are the same as for the primary stability testing. The tablets were placed in open petri dishes with a UV-transparent cover for 24 hours and exposed to >1.2 million lux hours and a near-UV energy corresponding to >200 $Wh/m^2$. The reference sample was covered with aluminium foil.

There were not any significant changes in the test parameters (including Description, Assay, Degradation Product and Drug Release) occurred during the Photostability study.

**(b) Summary of accelerated and long term testing (e.g., studies conducted, protocols used, results obtained):**

**(i) Description of stability study details:**

| Storage Conditions (˚C, % RH, light) | Strength and Batch Number | Batch Size | Container Closure System | Completed (and Proposed) Test Intervals |
|---|---|---|---|---|
| 40°C ± 2°C/75% RH ± 5%<br>30°C ± 2°C/60% RH ± 5%*<br>25°C ± 2°C/60% RH ± 5% | 10 mg **<br>A10-001 | 100,000 units | HDPE bottles of 100 | 0, 3, 6 months<br>(0, 3, 6, 9, 12 months)<br>0, 3, 6, 9, 12, 18, 24, 36 months |
| 40°C ± 2°C/75% RH ± 5%<br>30°C ± 2°C/60% RH ± 5%*<br>25°C ± 2°C/60% RH ± 5% | 25 mg<br>A25-001 | 100,000 units | HDPE bottles of 100 | 0, 3, 6 months<br>(0, 3, 6, 9, 12 months)<br>0, 3, 6, 9, 12, (18), (24), (36) months |
| 40°C ± 2°C/75% RH ± 5%<br>30°C ± 2°C/60% RH ± 5%*<br>25°C ± 2°C/60% RH ± 5% | 25 mg<br>A25-002 | 100,000 units | HDPE bottles of 100 | 0, 3, 6 months<br>(0, 3, 6, 9, 12 months)<br>0, 3, 6, 9, 12, (18), (24), (36) months |
| 40°C ± 2°C/75% RH ± 5%<br>30°C ± 2°C/60% RH ± 5%*<br>25°C ± 2°C/60% RH ± 5% | 50 mg<br>A50-001 | 100,000 units | HDPE bottles of 100 | 0, 3, 6 months<br>(0, 3, 6, 9, 12 months)<br>0, 3, 6, 9, 12, (18), (24), (36) months |
| 40°C ± 2°C/75% RH ± 5%<br>30°C ± 2°C/60% RH ± 5%*<br>25°C ± 2°C/60% RH ± 5% | 50 mg<br>A50-002 | 100,000 units | HDPE bottles of 100 | 0, 3, 6 months<br>(0, 3, 6, 9, 12 months)<br>0, 3, 6, 9, 12, (18), (24), (36) months |

| Storage Conditions (°C, % RH, light) | Strength and Batch Number | Batch Size | Container Closure System | Completed (and Proposed) Test Intervals |
|---|---|---|---|---|
| 40°C ± 2°C/75% RH ± 5%<br>30°C ± 2°C/60% RH ± 5%*<br>25°C ± 2°C/60% RH ± 5% | 75 mg<br>A75-001 | 100,000 units | HDPE bottles of 100 | 0, 3, 6 months<br>(0, 3, 6, 9, 12 months)<br>0, 3, 6, 9, 12, (18), (24), (36) months |
| 40°C ± 2°C/75% RH ± 5%<br>30°C ± 2°C/60% RH ± 5%*<br>25°C ± 2°C/60% RH ± 5% | 75 mg<br>A75-002 | 100,000 units | HDPE bottles of 100 | 0, 3, 6 months<br>(0, 3, 6, 9, 12 months)<br>0, 3, 6, 9, 12, (18), (24), (36) months |
| 40°C ± 2°C/75% RH ± 5%<br>30°C ± 2°C/75% RH ± 5%*<br>25°C ± 2°C/60% RH ± 5% | 25 mg<br>A25-002 | 100,000 units | HDPE Blisters | 0, 3, 6 months<br>(0, 3, 6, 9, 12 months)<br>0, 3, 6, 9, 12, (18), (24), (36) months |
| 40°C ± 2°C/75% RH ± 5%<br>30°C ± 2°C/75% RH ± 5%*<br>25°C ± 2°C/60% RH ± 5% | 50 mg<br>A50-002 | 100,000 units | HDPE Blisters | 0, 3, 6 months<br>(0, 3, 6, 9, 12 months)<br>0, 3, 6, 9, 12, (18), (24), (36) months |
| 40°C ± 2°C/75% RH ± 5%<br>30°C ± 2°C/60% RH ± 5%*<br>25°C ± 2°C/60% RH ± 5% | 75 mg<br>A75-002 | 100,000 units | HDPE Blisters | 0, 3, 6 months<br>(0, 3, 6, 9, 12 months)<br>0, 3, 6, 9, 12, (18), (24), (36) months |

* Samples will be pulled on their scheduled pull date. Samples at the intermediate condition are only tested if the product from the accelerated studies meets the "significant change" criteria as defined in ICH's Q1A guideline.
** Data on the 10 mg strength is provided as supporting data only (the 10 mg strength is approved for the Australian market and not proposed for the Canadian market).

The above batches were manufactured using six granulation blends. These granulation blend were compressed as follows:

(L) GB-001: A25-001
(L) GB-002: A50-001 and A50-002
(L) GB-003: A50-001 and A50-002
(L) GB-004: A75-001, A75-002, and A75-003
(L) GB-005: A75-001, A75-002, and A75-003
(L) GB-006: A75-001, A75-002, and A75-003

**(ii) Summary and discussion of stability study results:**

| Test | Acceptance Criteria | Results/Observations |
|---|---|---|
| Description[a,b] | see Module 2.3.P.5.1 | 25 mg, 50 mg and 75 mg:<br>Throughout the 12 month storage period, the appearance of the tablets complied with the specification irrespective of the storage conditions |
| Identification[a] | A: IR conforms<br>B: HPLC conforms | not performed |
| Average Mass (of 10 tablets)[c] | 25 mg: 110 mg ± 3%<br>50 mg: 220 mg ± 3%<br>75 mg: 330 mg ± 3% | not performed |
| Moisture[a,b] | NMT 4.5% | slight increase in moisture observed during accelerated studies (e.g., initially: 1.0%, after 3 months: 2.5%, increase of 1.5%); increase not observed on LT studies |

| Test | Acceptance Criteria | Results/Observations |
|---|---|---|
| Uniformity of Dosage Units (Content Uniformity)[a] | meets USP requirements | not performed |
| Assay (ambrosol (base) per tablet)[a,b] | Shelf-life: 90.0% to 110.0% of LC | 25 mg, 50 mg and 75 mg: Conforms.<br>The lowest result was 96.5 % (25 mg batch, blisters in accelerated condition), and the highest 98.5 %. |
| Drug Release[a,b]<br>(App. 1, 50 rpm, 1L)<br>Acid stage (pH 1.2)<br>Buffer stage (pH 6.8) | <br><br>NMT 10% in 2 hours<br>NLT 75% (Q) in 30 minutes | 25 mg, 50 mg and 75 mg:<br>The resistance to gastric fluid (0.1N HCl) was proven for all tested tablets (max. release in acid phase was 3%);<br>The dissolved quantity of active determined at pH 6.8 was found between 83% and 88% across all storage conditions for the 25 mg tablet; between 79% and 85% across all storage conditions for the 50 mg tablet, and between 80% and 84% across all storage conditions for the 75 mg tablet. |
| Degradation Products[b] | RC2: NMT 0.5%<br>Indiv. unspecified: NMT 0.2%<br>Total: NMT 1.0% | slight increase in concentration of RC2 under accelerated condition with a maximum level of 0.4% observed; no significant trends were noted in long term stability with a maximum level of 0.3%;<br>all individual unspec. <0.2%;<br>slight increase in Total Degr. Products under accelerated conditions (e.g., initially: 0.4%, after 3 months: 0.8%, increase of 0.4%); increase not observed on LT studies |

a = tested on release
b = tested on stability
c = tested in-process

**(c) Proposed storage conditions and shelf life (and in-use storage conditions and in-use period, if applicable):**

The above summarized results show that the 25 mg, 50 mg and 75 mg enteric-coated tablets are stable with respect to their chemical purity in the proposed container closure systems under accelerated (3 months at 40ºC/75% RH) and long term conditions (12 months at 25ºC/60%RH).

An extrapolated shelf life of 24 months is proposed based on a statistical assessment of the results in accordance with ICH's Q1E Evaluation of Stability Data guideline. The statistical assessment can be found in Module 3.2.P.8.1, pages 42-52.

| Container Closure System | Storage Conditions | Shelf Life |
|---|---|---|
| HDPE bottles of 100's with PP cap (bottles of 100's) | Store at controlled room temperature (15-30ºC). Protect from light. | 24 months |
| PVC/Aluminum foil blister (5x10's) | Store at controlled room temperature (15-30ºC). Protect from light. | 24 months |

The above recommended storage condition is consistent with that included in the Product Monograph.

### *2.3.P.8.2 Post-approval Stability Protocol and Stability Commitment (Ambrosia® Delayed-release Tablets, EC Tablets)*

**(a) Stability protocol for commitment batches:**

| Protocol Parameter | Description |
|---|---|
| **Storage conditions (including tolerances)** | 25°C ± 2°C/60% RH ± 5% |
| **Testing frequency** | 0, 3, 6, 9, 12, 18, 24, 36 months |
| **Number of batches per strength and batch sizes** | first three production batches (1,000,000 units) each of the 25 and 75 mg strengths will be added to the stability programme |
| **Container closure system(s)** | same as described in 2.3.P.7 |
| **Tests and acceptance criteria** | stability tests described in 2.3.P.5.1 |
| **Other** | N/A |

**(b) Stability protocol for continuing (i.e., ongoing) batches:**

| Protocol Parameter | Description |
|---|---|
| **Storage conditions (including tolerances)** | 25°C ± 2°C/60% RH ± 5% |
| **Testing frequency** | 0, 3, 6, 9, 12, 18, 24, 36 months |
| **Number of batches per strength and batch sizes** | one production batch (1,000,000 units) per year each of the 25 and 75 mg strengths will be added to the stability programme |
| **Container closure system(s)** | same as described in 2.3.P.7 |
| **Tests and acceptance criteria** | stability tests described in 2.3.P.5.1 |
| **Other** | N/A |

### *2.3.P.8.3 Stability Data (Ambrosia® Delayed-release Tablets, EC Tablets)*

**(a) The actual stability results (i.e., raw data) should be provided in Module 3.**

The actual stability results (i.e., raw data) can be found in Module 3.2.P.8.3, pages 4-80.

**(b) Summary of analytical procedures and validation information for those procedures not previously summarized in 2.3.P.5 (e.g., analytical procedures used only for stability studies):**

N/A (there were not any analytical procedures used that were not previously summarized in 2.3.P.5).

**(c) Bracketing and matrixing design and justification for commitment and/or continuing (i.e., ongoing) batches, if applicable:**

The cores for the three strengths are compositionally proportional with only minor differences in the overall formulations (e.g., differences in colouring agents for the coating). As such, stability studies for the commitment and ongoing batches are proposed to be performed on the highest (75 mg) and lowest (25 mg) strengths. Supporting data has been provided on the intermediate (bracketed) 50 mg strength showing that there are not any incompatibilities with the formulation (e.g., the active ingredient with the excipients).

This bracketing design on strengths is consistent with ICH's Q1D Bracketing and Matrixing guideline.

## 2.3.A APPENDICES

### 2.3.A.1 Facilities and Equipment (Ambrosia® Delayed-release Tablets, Drugs 'R' Us)

**(a) Summary of information on facilities and equipment, in addition to the information provided in other sections of the submission:**

N/A (there is not information on facilities and equipment, in addition to the information provided in other sections of this submission).

### 2.3.A.2 Adventitious Agents Safety Evaluation (Ambrosia® Delayed-release Tablets, Drugs 'R' Us)

**(a) Summary of the information assessing the risk with respect to potential contamination with adventitious agents:**

N/A (there is not potential contamination with adventitious agents).

### 2.3.A.3 Excipients

**(a) Summary of the details of manufacture, characterization, and controls, with cross references to supporting safety data (nonclinical and/or clinical) for the novel excipients:**

N/A (there are not any "novel" excipients).

**(b) Summary of significant amount of data for noncompendial, nonnovel excipients:**

N/A (there are not significant amounts of data for noncompendial, nonnovel excipients).

## 2.3.R REGIONAL INFORMATION

### 2.3.R.1 Production Documentation (Ambrosia® Delayed-release Tablets, EC Tablets)

#### *2.3.R.1.1 Executed Production Documents (Ambrosia® Delayed-release Tablets, EC Tablets)*

**(a) List of batches (including strengths) for which executed production documents have been provided (e.g., pivotal clinical and comparative bioequivalence batches):**

Executed production documents have been provided on all the lots used in the pivotal clinical and comparative bioequivalence studies as well as one representative batch of each strength, i.e.,:

| Strength | Drug Product Batch No. | Type of Study | Location |
|---|---|---|---|
| 25 mg | A25-001 | (representative of 25 mg strength) | Module 3.2.R.1.1, pages 2-50 |
| 50 mg | A50-001 | (representative of 50 mg strength) | Module 3.2.R.1.1, pages 51-100 |
| 75 mg | A75-001 | Pivotal clinical study and bridging *in vivo* bioequivalence | Module 3.2.R.1.1, pages 101-150 |
| 75 mg | A75-002 | Bridging *in vivo* bioequivalence | Module 3.2.R.1.1, pages 151-200 |

***2.3.R.1.2 Master Production Documents (Ambrosia® Delayed-release Tablets, EC Tablets)***

**(a) The blank master production documents for each strength, proposed batch size, and manufacturing facility should be provided in Module 3.**

Copies of the blank master production documents have been provided for each strength, proposed batch size (i.e., 1,000,000 units), and both manufacturing facilities (see Module 3.2.R.1.2, pages 2-150).

**2.3.R.2 Medical Devices (Ambrosia® Delayed-release Tablets, EC Tablets)**

**(a) Summary of the description and details on medical devices used to deliver the dosage form that are external to the drug product (e.g., eye droppers, plastic applicators):**

N/A (there are not any medical devices used to deliver the dosage form).

**Index of Attachments**

| Attachment | Summary | Analytical Procedure |
|---|---|---|
| 1 | method | Assay: HPLC/House/TM-DS/DP-03, ver. 1.1 |
| 2 | validation report | |
| 3 | method | Related Substances: HPLC/House/TM-DS/DP-05, ver. 2.0 |
| 4 | validation report | |
| 5 | method | Residual Solvents: GC/House/TM-DS-04, ver. 1.0 |
| 6 | validation report | |
| 7 | method | Polymorphic Content: XRD/House/TM-DS-02, ver. 1.0 |
| 8 | validation report | |
| 9 | method | Drug Release: UV/House/TM-DP-06, ver. 1.0 |
| 10 | validation report | |

| **ATTACHMENT NUMBER:** | 1 |
|---|---|

| **Method name:** | Identification, Assay, and Content Uniformity in Ambrosol Drug Substance and Tablets | | |
|---|---|---|---|
| **Method code:** | TM-DS/DP-03 | **Version and/or Date:** | Version 1.1 |
| Column(s) / temperature (if other than ambient): | Luna C8 or Luna C8 (2), 5µ, 150 X 4.6 mm, Phenomenex (Security Guard C8 4 mm L30 mm ID guard column is recommended).<br>Column temperature 30°C | | |
| Mobile phase (specify gradient program, if applicable): | Buffer* : Acetonitrile : Methanol (48 : 27 : 25)<br>*Buffer Preparation: Dissolve 3.48 g dipotassium hydrogen phosphate (0.02M), adjust to pH 6.4 with ortho-phosphoric acid. | | |
| Detector (and wavelength, if applicable): | UV 280 nm | | |
| Flow rate: | 1.0 mL/min. | | |
| Injection volume: | 10 µL | | |
| Sample solution concentration (expressed as mg/mL, let this be termed "A"): | 0.2 mg/mL Ambrosol | | |
| Reference solution concentration (expressed as mg/mL and as % of "A"): | 0.2 mg/mL (working standard)<br>100 % of A | | |
| System suitability solution concentration (expressed as mg/mL and as % of "A"): | System Suitability Solution<br>0.0013 mg/mL<br>0.65% | Diluted Standard Solution<br>0.01 mg/mL<br>5.0 % of A | Sensitivity Standard Solution<br>0.0005 mg/mL<br>0.25 % of A |
| System suitability tests (tests and acceptance criteria): | Inject Sensitivity Standard Solution. The ambrosol peak must be clearly detected (signal to noise ratio not less than 3).<br><br>Inject System Suitability Solution. The resolution between the two largest peaks of degradation products (RC 1 and RC 2), should not be less than 3.5.<br><br>Inject Diluted Standard Solution. The relative standard deviation for six replicate injections is NMT 1.0% (for DS assay) or NMT 2.0% (for DP assay).<br><br>Inject Working Standard Solution. The tailing of ambrosol peak should not be less than 0.9 and not more than 2.0.<br><br>Check that the ratio between normalized ambrosol responses in Working and Diluted Standard Solutions is between 16.0 and 17.4. The test provides that analysis is performed within linearity range. | | |
| Method of quantification: | Ambrosol quantified against Ambrosol in Reference solution | | |
| Other information: | Not applicable | | |

| ATTACHMENT NUMBER: | 2 |
|---|---|

| Validation Report Name: | Identification, Assay, and Content Uniformity in Ambrosol Drug Substance and Tablets (VR-TM-DS/DP-03, Version 1.1) |
|---|---|

| Validation Summary | | Volume/Page: | 3.2.S.4.3; Page 12-31 | |
|---|---|---|---|---|
| **Analytes:** | | Ambrosol | | |
| Typical retention times (RT) or response factors (RF): | | 11.1 | | |
| Relative retention times ($RT_{Imp.}/RT_{Dr.Sub.\ or\ Int.\ Std.}$): | | N/A | | |
| Relative response factor ($RF_{Imp.}/RF_{Dr.Sub.}$): | | N/A | | |
| **Specificity:** | | The selectivity of the method was tested by injecting blank, placebo, typical sample and spiked sample solutions. The method was found to be selective for its purpose, and no interfering peaks were observed. | | |
| **Linearity / Range:** | Number of concentrations:<br>Range (expressed as % "A"):<br>Slope:<br>Y-intercept:<br>Correlation coefficient ($r^2$) : | 5<br>50% - 150% (corresponds to 0.1 - 0.3 mg/mL)<br>3859123<br>0.582779<br>0.999892 | | |
| **Accuracy:** | Conc.(s) (expressed as % "A"):<br>Number of replicates:<br>Percent recovery (avg/RSD): | 70%<br>3<br>102.1% / 0.64% | 100%<br>3<br>100.8% / 0.06% | 130%<br>3<br>100.6% / 0.98% |
| **Precision / Repeatability:**<br>(intra-assay precision) | Conc.(s) (expressed as % "A"):<br>Number of replicates:<br>Result (avg/RSD): | 0.05mg tablet<br>6<br>97.0% / 1.4% | 0.25mg tablet<br>6<br>97.3% / 0.7% | 1mg tablet<br>6<br>101.2% / 0.4% |
| **Precision / Intermediate Precision:**<br>(days/analysts/equipment) | Parameter(s) altered:<br><br>Result (avg/RSD): | (days/analysts/equipment)<br><br>**Validation for Assay**<br>**Set No. 1:**<br>0.05mg Tablet: Avg. 94.2%; RSD 0.6%<br>0.25mg Tablet: Avg. 97.3%; RSD 0.7%<br>1mg Tablet: Avg. 98.3%; RSD 0.6%<br><br>**Set No. 2:**<br>0.05mg Tablet: Avg. 94.8%; RSD 1.3%<br>0.25mg Tablet: Avg. 96.9%; RSD 1.6%<br>1mg Tablet: Avg. 97.5%; RSD 0.5% | | |
| | | **Validation for Identification**<br>The retention time of Ambrosol was not found to differ by more than 2%. | | |
| | | **Validation for Content Uniformity**<br>**Set No. 1:**<br>0.05mg Tablet: Avg. 97.8%; RSD 0.7%<br>0.25mg Tablet: Avg. 99.1%; RSD 1.5%<br>1mg Tablet: Avg. 99.3%; RSD 1.0%<br><br>**Set No. 2:**<br>0.05mg Tablet: Avg. 97.8%; RSD 4.5%<br>0.25mg Tablet: Avg. 97.3%; RSD 0.4%<br>1mg Tablet: Avg. 102.1%; RSD 0.6% | | |
| **Limit of Detection (LOD):** | | 0.25% Concentration Level | | |
| **Limit of Quantitation (LOQ):** | | 0.5% Concentration Level | | |

| Validation Summary | | Volume/Page: | 3.2.S.4.3; Page 12-31 |
|---|---|---|---|
| **Robustness:** | Stability of solutions: | Ambrosol standard stock solution is stable for at least 9 days under normal laboratory conditions. Sample solutions may be considered stable for 2 days under normal conditions. | |
| | Other variables/effects: | The method is robust while varying flow rate, buffer pH, mobile phase composition; different sample volumes, varying detector settings & using different LUNA C8 columns. | |
| **Typical chromatograms or spectra may be found in:** | | 3.2.S.4.3, p 10 | |
| **Company(s) responsible for method validation:** | | Drugs 'R' Us | |
| **Other information:** | | | |

| **ATTACHMENT NUMBER:** | 3 |
|---|---|

| **Method name:** | HPLC Quantitation of Related Substances Present in Drug Substance and Drug Product | | |
|---|---|---|---|
| **Method code:** | TM-DS/DP-05 | **Version and/or Date:** | 2 |
| Column(s) / temperature (if other than ambient): | Waters XTerra RP18, 10 cm (L) x 4.6 mm (ID), 3.5 µm | | |
| Mobile phase (specify gradient program, if applicable): | pH 7.20 buffer (35mM sodium phosphate monobasic dihydrate) and methanol = 40:60 (v/v)<br><br>Total run time = 30 minutes | | |
| Detector (and wavelength, if applicable): | Waters Model 486 variable wavelength detector, or equivalent, set at 263 nm | | |
| Flow rate: | 1.0 mL/min | | |
| Injection volume: | 20 µL | | |
| Sample solution concentration (expressed as mg/mL, let this be termed "A"): | 0.20 mg/mL Drug Substance (100% A)<br>1 mg/mL Drug Product (100% A) | | |
| Reference solution concentration (expressed as mg/mL and as % of "A"): | Working Reference Standard Solution<br>0.0002 mg/mL, 0.1% A (Drug Substance)<br>0.0004 mg/mL, 0.2% A (Drug Product) | | |
| System suitability solution concentration (expressed as mg/mL and as % of "A"): | Sensitivity solution 0.3 µg/mL, 0.05% A<br>Identification Solution: each impurity 0.1% A<br>Working Reference Standard Solution (as above) | | |
| System suitability tests (tests and acceptance criteria): | ID solution:<br>Resolution $R_1$ (between impurities RC1 and RC2) and resolution $R_2$ (between ambrosol and RC3) not less than 1.5<br><br>Sensitivity solution:<br>S/N ratio NLT 10<br><br>Working Reference Standard:<br>Plate count not less than 2000 for ambrosol and relative standard deviation of ambrosol peak responses for six consecutive injections is not more than 5%. | | |
| Method of quantification: | Quantitates impurities RC1-3 using relative response factor correction values against drug substance in Working Reference Standard Solution. Other impurities quantified as unspecified impurities against ambrosol in Working Reference Standard Solution. | | |
| Other information: | Method derived from monograph (USP 28 Supplement 2) with modification of column type and mobile phase composition.<br>Related substance, RC1, is only reported for the drug substance. | | |

| ATTACHMENT NUMBER: | 4 |
|---|---|

**Validation Report Name:** **HPLC Quantitation of Related Substances Present in Drug Substance and Drug Product (VR-TM-DS/DP-05, Version 2.0)**

| Validation Summary | | Volume/Page: 3.2.S.4.3 p. 47-99 | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Analytes:** | | RC1 | | | RC2 | | | Ambrosol |
| Typical retention times (RT) or response factors (RF): | | RT=3.1 | | | RT=3.8 | | | RT=11.2 |
| Relative retention times ($RT_{Imp.}/RT_{Dr.Sub.\ or\ Int.\ Std.}$): | | 0.28 | | | 0.33 | | | 1 |
| Relative response factor ($RF_{Imp.}/RF_{Dr.Sub.}$): | | 0.67 | | | 1.38 | | | 1 |
| **Specificity:** | | Chromatograms submitted demonstrate the method is capable of resolving ambrosol from a large number of degradation products and known impurities RC 1-3.<br>Chromatography of placebo preparations demonstrated no significant interference with the analytes of interest. | | | | | | |
| **Linearity/ Range:** | Number of concs.:<br>Range ( % of "A"):<br>Slope:<br>Y-intercept:<br>Correlation coeff. ($r^2$) : | 5<br>0.02-0.6%<br>$1.174284x10^6$<br>$2.242161x10^3$<br>0.999778 | | | 5<br>0.05-1.5%<br>$5.677927x10^5$<br>$4.143966x10^2$<br>0.999998 | | | 5<br>0.02-1.0%<br>$7.817301x10^5$<br>$1.069107x10^3$<br>0.998506 |
| **Accuracy:** | Conc.(s) ( % of "A"):<br>Number of replicates:<br>Percent recovery (avg/RSD): | 0.05%<br>3<br>88.0/ 3.1 | 0.2%<br>3<br>92.5/ 1.0 | 0.6%<br>3<br>98.6/ 1.1 | 0.05%<br>3<br>105.6/ 8.6 | 0.4%<br>3<br>97.6/ 4.9 | 1.5%<br>3<br>104.7/ 0.9 | 0.2% (spiked placebo*)<br>6<br>104%/ 3.9% |
| **Precision / Repeatability:** (intra-assay precision) | Conc.(s) (% of "A"):<br>Number of replicates:<br>Result (avg/RSD): | 0.2%<br>6<br>0.19% / 3.1% RSD | | | 0.3%<br>6<br>0.32%/5.1% RSD | | | 0.2% (spiked placebo*)<br>6<br>0.21%/4.8% RSD |
| **Precision / Intermediate Precision:** | Parameter(s) altered:<br>Result (avg/RSD): | Day/analyst/equipment<br>Total Impurities: 2.206% / 0.8% RSD; Active: 0.24%/5.1% RSD | | | | | | |
| **Limit of Detection (LOD):** | | <0.05% of A | | | <0.05% of A | | | <0.05% of A |
| **Limit of Quantitation (LOQ):** | | 0.05% of A | | | 0.05% of A | | | 0.05% of A |
| **Robustness:** | Stability of solutions:<br>Other variables/effects: | Standard solution stability was demonstrated by repeated injection over a period of 40 hours. Sample solution stability was demonstrated by repeated injection over a period of 65 hours.<br>Robustness of sample preparation with respect to filtration was shown by comparing results obtained using either Nylon or PTFE filters. No significant difference in results was observed.<br>Mobile phase composition was varied by ±5%, Column temperature by ±5˚C without significant difference in results. | | | | | | |
| **Typical chromatograms or spectra may be found in:** | | 3.2.S.4.2 p 16-25 | | | | | | |
| **Company(s) responsible for method validation:** | | Drugs 'R' Us | | | | | | |

| Validation Summary | **Volume/Page:** 3.2.S.4.3 p. 47-99 |
|---|---|
| **Other information:** | |

# % RSD is slightly above the criteria of 10% at the limit of quantitation recommended in the *Acceptable Methods* guideline, however it is within acceptable limits at the proposed specification limit of 0.2%, therefore it is not considered to be critical and will not affect the quality of the product, therefore it was accepted.

* The placebo used was for the lowest strength tablets as this was considered a worst case scenario, where the ratio of active to excipients was lowest.

| ATTACHMENT NUMBER: | 5 |
|---|---|

| Method name: | GC Head Space Determination of Residual Solvents in Ambrosol HCl Drug Substance | | |
|---|---|---|---|
| **Method code:** | TM-DS-04 | **Version and/or Date:** | Version 1.0 |
| Column / temperature (specify temperature program, if applicable): | DB-624, 0.53 mm x 30 m x 3 µm. | | |
| Carrier and auxiliary gas (type / flow rate): | Air: 450 mL/minute<br>Hydrogen: 40 mL/minute | | |
| Detector (type / temperature): | GC system; 200°C | | |
| Injection (volume / temperature): | 1 mL (headspace vial); 180°C | | |
| Sample solution concentration (expressed as mg/mL, let this be termed "A"): | ***Sample preparation***<br>Weigh 100 mg of Amrosol HCl raw material into each of two headspace vials. Add 1 mL of DMSO. Cap immediately. | | |
| Reference solution concentration (expressed as mg/mL and as % of "A"): | ***Standard stock solution A***<br>In a 100 mL volumetric flask, add 50 mL of dimethylsulfoxide (DMSO). Using a volumetric pipette, add 1 mL of ethanol and acetic acid). Complete to volume with DMSO.<br>***Standard stock solution B***<br>In a 100 mL volumetric flask, add 50 mL of DMSO. Using a volumetric pipette, add 3 mL of dichloromethane. Complete to volume with DMSO. Pipette 2 mL of this solution into 25 mL volumetric flask and complete to volume with DMSO.<br>***Standard stock solution***<br>Pipet 3 mL of standard stock solution A and 1 mL of standard stock solution B to a 50 mL volumetric flask and complete to volume with DMSO.<br>***Standard Preparation***<br>Accurately weigh 100 mg of Ambrosol HCl drug substance into eight headspace vials. Pipette 1 mL of standard stock solution to each vial and cap immediately. | | |
| System suitability solution concentration (expressed as mg/mL and as % of "A"): | Standard Preparation | | |
| System suitability tests (tests and acceptance criteria): | Calculation of the reproducibility is done on the basis of six replicate injections of the standard solution. Tailing factor and retention time are determined on the basis the first injection of the standard solution. The following criteria must be met:<br>a) Relative Standard Deviation (RSD≤ 5.0%)<br>b) Tailing Factor (T≤ 2.0) | | |
| Method of quantification: | Quantified against solvent in reference standard. | | |
| Other information: | Average velocity: 40 cm/sec<br>Split ratio: 20:1<br>Make-up gas (Helium): 30 mL/minute<br>Oven: 40 °C for 7 min., ramp 20 °C/minute to 220 °C | | |

| ATTACHMENT NUMBER: | 6 |
|---|---|

| Validation Report Name: | GC Head Space Determination of Residual Solvents in Ambrosol HCl Drug Substance (VR-TM-DS-04 ) | | | |
|---|---|---|---|---|
| **Validation Summary** | | **Volume/Page:** | 3.2.S.4.3, p.109-131 | |
| **Analytes:** | | Acetic Acid | Dichloromethane | Ethanol |
| Typical retention times (RT) or response factors (RF): | | 3.4 min | 3.8 min | 7.1 min |
| Relative retention times ($RT_{Imp.}/RT_{Dr.Sub.\ or\ Int.\ Std.}$): | | - - - - - | - - - - - | - - - - - |
| Relative response factor ($RF_{Imp.}/RF_{Dr.Sub.}$): | | - - - - - | - - - - - | - - - - - |
| **Specificity:** | | The chromatogram of the diluting solvent was free of interference when compared with the chromatogram of a standard solution. Drug substance spiked with solvent gave quantitative recoveries. | | |
| **Linearity / Range:** | Number of concentrations:<br>Range (expressed as % "A"):<br>Slope:<br>Y-intercept:<br>Correlation coefficient ($r^2$) : | 9<br>LOQ-200%<br>0.1661<br>-0.6073<br>1.000 | 7<br>LOQ-200%<br>0.1349<br>+0.1930<br>1.000 | 9<br>LOQ-200%<br>0.1187<br>-0.2014<br>1.000 |
| **Accuracy:** | Conc.(s) (expressed as % "A"):<br>Number of replicates:<br>Percent recovery (avg/RSD): | 20, 100, 200%<br>3, 6, 3<br>101.1% | 20, 100, 200%<br>3, 6, 3<br>100.0% | 20, 100, 200%<br>3, 6, 3<br>101.7% |
| **Precision / Repeatability:**<br>(intra-assay precision) | Conc.(s) (expressed as % "A"):<br>Number of replicates:<br>Result (avg/RSD): | 1000, 5000, 10000 ppm<br>3, 6, 3<br>0.51, 0.38, 1.39 % | 120, 600, 1200 ppm<br>3, 6, 3<br>0.79, 0.31, 0.52% | 1000, 5000, 10000 ppm<br>3, 6, 3<br>0.12, 0.53, 2.27% |
| **Precision / Intermediate Precision:**<br>(days/analysts/equipment) | Parameter(s) altered:<br>Result (avg/RSD): | The ruggedness of the method was evaluated by a second analyst, whose work was independent from the accuracy study. This implies the injection of a freshly prepared standard solution and reconstituted samples on a different GC system and column. The average recovery of each solvent was measured in reconstituted sample preparations spiked at 100% of their validation limit.<br>The average recovery at each level for all residual solvents, is within the acceptance limit (90-110%). | | |
| | | 99.8 % | 99.5% | 100.0% |
| **Limit of Detection (LOD):** | | 24 ppm | 13 ppm | 24 ppm |
| **Limit of Quantitation (LOQ):** | | 48 ppm | 32 ppm | 97 ppm |
| **Robustness:** | Stability of solutions:<br>Other variables/effects: | ***Stability of the solution***<br>The standard solution should be used on the day of analysis, then discarded. Standards and samples that have already been transferred to headspace vials should be injected within 48 hours. Headspace vials must not be reinjected since the vapour equilibrium within the vial will have shifted. | | |
| **Typical chromatograms or spectra may be found in:** | | 3.2.S.4.3 p. 52 - 68 | | |
| **Company(s) responsible for method validation:** | | Testy Inc. | | |
| **Other information:** | | This method was also validated for quantification of Toluene, however results are not summarized in these tables. | | |

| ATTACHMENT NUMBER: | 7 |
|---|---|

| Method name: | Polymorphic Content in Ambrosol HCl Drug Substance | | |
|---|---|---|---|
| Method code: | TM-DS-02 | Version and/or Date: | Version 1.0 |

[Note to Reader: illustrative examples for this section have not been included at this time].

| ATTACHMENT NUMBER: | 8 |
|---|---|

| Validation Report Name: Polymorphic Content in Drug Substance (VR-TM-DS-02 Version 1.0) |
|---|

[Note to Reader: illustrative examples for this section have not been included at this time].

| **ATTACHMENT NUMBER:** | 9 |
|---|---|

| **Method name:** | Dissolution Test of Ambrosol HCl Tablets | | |
|---|---|---|---|
| **Method code:** | TM-DP-06 | **Version and/or Date:** | Version 1.0 |
| Detection wavelength: | 369 nm | | |
| Sample solution concentration<br>(expressed as mg/mL, let this be termed "A"): | 25 mg: 0.025 mg/mL<br>50 mg: 0.05 mg/mL<br>75 mg: 0.075 mg/mL | | |
| Reference solution concentration<br>(expressed as mg/mL and as % of "A"): | 25 mg: 0.025 mg/mL<br>50 mg: 0.005 mg/mL<br>75 mg: 0.075 mg/mL<br>100 % of A | | |
| Method of quantification: | Ambrosol quantified against Ambrosol in reference solution | | |
| Other information: | Drug Release<br>(Apparatus 1, 50 rpm, Temperature 37°C)<br>Acid stage (HCl pH 1.2) - 1 L<br>Phosphate Buffer stage (pH 6.8) - 1 L | | |

| ATTACHMENT NUMBER: | 10 |
|---|---|

**Validation Report Name: Dissolution Test of Ambrosol Tablets (VR-TM-DP-06 Version 1.0)**

| Validation Summary | | Volume/Page: | 3.2.P.4.3; Page 20-25 | |
|---|---|---|---|---|
| **Analytes:** | | Ambrosol | | |
| **Specificity:** | | The selectivity of the method was tested by analyzing mixtures of non-actives (placebo), versus standard solution. No interfering absorption at 369 nm was observed in the placebo and dissolution medium; the method was found to be specific for its purpose. | | |
| **Linearity / Range:** | Number of concentrations:<br>Range (expressed as % "A"):<br>Slope:<br>Y-intercept:<br>Correlation coefficient ($r^2$) : | 5<br>50% (of 25 mg) - 120% (of 75 mg tablet) (0.025 - 0.09 mg/mL)<br>1995568216<br>3865.34<br>0.9999 | | |
| **Accuracy:** | Conc.(s) (expressed as % "A"):<br><br>Number of replicates:<br>Percent recovery (avg/RSD): | 100% of the 75mg/tablet dose<br>2<br>97.0% / 0.9% | 80% (Q+5%) of the 50mg/tablet dose<br>2<br>98.7% / 1.2% | 50% (Q-25%) of 25mg/tablet dose<br>2<br>100.4% / 0.4% |
| **Precision / Repeatability:** (intra-assay precision) | Conc.(s) (expressed as % "A"):<br>Number of replicates:<br>Result (avg/RSD): | 25mg per tablet<br>6<br>91% / 1.7% | 50mg per tablet<br>6<br>92% / 3.3% | 75mg per tablet<br>6<br>91% / 3.1% |
| **Precision / Intermediate Precision:** (days/analysts/equipment) | Parameter(s) altered:<br><br>Result (avg/RSD): | 25mg per tablet (days/analysts/ equipment)<br>97% / 1.8% | 50mg per tablet (days/analysts/ equipment)<br>92% / 2.4% | 75mg per tablet (days/analysts/ equipment)<br>98% / 1.2% |
| **Limit of Detection (LOD):** | | Not applicable | | |
| **Limit of Quantitation (LOQ):** | | Not applicable | | |
| **Robustness:** | Stability of solutions:<br><br>Other variables/effects: | The standard solution is stable for at least 12 days at room temperature. Sample solutions are stable for at least 1 day at room temperature.<br>Robust for change in temperature (±5%), Dissolution medium (Phosphate Buffer pH 6.5 -7.0).<br>***Filtration Test:***<br>One portion of the 100% solution was filtered through a dissolution filter while another portion was centrifuged at 2500 rpm for 5 minutes. The solutions were analyzed and then compared.<br>The difference in recovery between the filtered and centrifuged sample preparations is within the acceptance limit (≤3%). | | |
| **Typical chromatograms or spectra may be found in:** | | 3.2.P.4.2 p 9 | | |
| **Company(s) responsible for method validation:** | | Drugs 'R' Us | | |
| **Other information:** | | Validation of the analytical methodology was performed with placebo tablets spiked with drug substance. Solution preparation was performed using the proposed dissolution apparatus. Development of the dissolution method is discussed in 3.2.PXX | | |