COMMON TECHNICAL DOSSIER

Module 2 – Common Technical Document summary		
2.1	CTD Table of contents (Modules 2-5)	
2.2	CTD introduction	
2.3	Quality over all summary	
2.4	Non clinical overview	
2.5	Clinical overview	
2.6	Non clinical summary	
2.7	Clinical summary	

Module 3 – Quality			
3.1	**Table of contents of module 3**		
3.2	**Body of data**		
3.2 S	**Drug Substance**		
3.2.S.1	**General information**		
	3.2.S.1.1	Nomenclature	
	3.2.S.1.2	Structure	
	3.2.S.1.3	General properties	
3.2.S.2	**Manufacture**		
	3.2.S.2.1	Manufacturer(s)	
	3.2.S.2.2	Description of manufacturing process and process controls	
	3.2.S.2.3	Control of materials	
	3.2.S.2.4	Controls of critical steps and intermediates	
	3.2.S.2.5	Process validation and/or evaluation	
	3.2.S.2.6	Manufacturing process development	
3.2.S.3	**Characterization**		
	3.2.S.3.1	Elucidation of structure and other characteristics	
	3.2.S.3.2	Impurities	
3.2.S.4	**Control of drug substance**		
	3.2.S.4.1	Specification	
	3.2.S.4.2	Analytical procedures	
	3.2.S.4.3	Validation of analytical procedures	
	3.2.S.4.4	Batch analyses	
	3.2.S.4.5	Justification of specification	
3.2.S.5	**Reference standards or materials**		
3.2.S.6	**Container closure system**		
3.2.S.7	**Stability**		
	3.2.S.7.1	Stability summary and conclusion	
	3.2.S.7.2	Post approval stability protocol and stability commitment	
	3.2.S.7.3	Stability data	
3.2.P	**Drug product**		
3.2.P.1	Description and composition of the drug product		
3.2.P.2	Pharmaceutical Development		
3.2.P.3	Manufacture		

	3.2.P.3.1	Manufacturer(s)	
	3.2.P.3.2	Batch formula	
	3.2.P.3.3	Description of manufacturing process and process controls	
	3.2.P.3.4	Controls of critical steps and intermediates	
	3.2.P.3.5	Process validation and/or evaluation	
3.2.P.4	Control of Excipient		
	3.2.P.4.1	Specifications	
	3.2.P.4.2	Analytical procedures	
	3.2.P.4.3	Validation of analytical procedures	
	3.2.P.4.4	Justifications of specifications	
	3.2.P.4.5	Excipient of human or animal origin	
	3.2.P.4.6	Novel Excipient	
3.2.P.5	Control of drug product		
	3.2.P.5.1	Specification(s)	
	3.2.P.5.2	Analytical procedures	
	3.2.P.5.3	Validation of analytical procedures	
	3.2.P.5.4	Batch analyses	
	3.2.P.5.5	Characterization of impurities	
	3.2.P.5.6	Justification of specification(s)	
3.2.P.6	Reference standards or materials		
3.2.P.7	Container closure system		
3.2.P.8	Stability		
	3.2.P.8.1	Stability summary and conclusion	
	3.2.P.8.2	Post approval stability protocol and stability commitment	
	3.2.P.8.3	Stability data	
3.2.A	Appendices		
	3.2.A.1	Facilities and equipments	
	3.2.A.2	Adventitious agents' safety evaluation	
	3.2.A.3	Excipient	
3.2.R	Regional information		
	3.2.R.1	Production documentation	
	3.2.R.1.1	Executed production documents	
	3.2.R.1.2	Master production documents	
	3.2.R.2	Analytical procedures and validation information	

Module 4- Nonclinical study report			
	4.1	Table of contents of module 4	
	4.2	Study report	
	4.3	Literature survey	

Module 5- Clinical study report		
5.0	Clinical Study Report	
5.1	Table of content	

5.2	Tabular Listing of All Clinical Studies		
5.3	Clinical Study Reports		
	5.3.1	Reports of Biopharmaceutics Studies	
	5.3.1.1	Bioavailability (BA) Study Reports	
	5.3.1.2	Comparative Bioavailability (BA) and Bioequivalence (BE) Study Reports	
	5.3.1.3	In vitro-In vivo Correlation Study Reports	
	5.3.1.4	Reports of Bioanalytical and Analytical Methods for Human Studies	
	5.3.2	Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials	
	5.3.3	Reports of Human Pharmacokinetic Studies	
	5.3.4	Reports of Human Pharmacodynamic Studies	
	5.3.5	Reports of Efficacy and Safety Studies	
	5.3.6	Reports of Post-marketing Experience	
	5.3.7	Case Report Forms and Individual Patient Listings	
5.4	Literature References		

2.2 CTD introduction

Proprietary Name

Paclimed 300mg

Non Proprietary Name of drug substance

Paclitaxel injection USP 300mg/50ml

Dosage form

Liquid injection

Strength

300mg

Route of administration

Intravenous

Indication

Ovarian carcinoma: in the first-line chemotherapy of ovarian cancer, paclitaxel is indicated for the treatment of patients with advanced carcinoma of the ovary or with residual disease (> 1 cm) after initial laparotomy, in combination with cisplatin.

In the second-line chemotherapy of ovarian cancer, paclitaxel is indicated for the treatment of metastatic carcinoma of the ovary after failure of standard, platinum containing therapy.

Breast carcinoma: in the adjuvant setting, Paclitaxel is indicated for the treatment of patients with node-positive breast carcinoma following anthracycline and cyclophosphamide (AC) therapy. Adjuvant treatment with Paclitaxel should be regarded as an alternative to extended AC therapy.

Paclitaxel is indicated for the initial treatment of locally advanced or metastatic breast cancer either in combination with an anthracycline in patients for whom anthracycline therapy is suitable, or in combination with trastuzumab, in patients who over-express HER-2 (human epidermal growth factor receptor 2) at a 3+ level as determined by immunohistochemistry and for whom an anthracycline is not suitable.

2.3 Quality overall summary

S Drug Substances

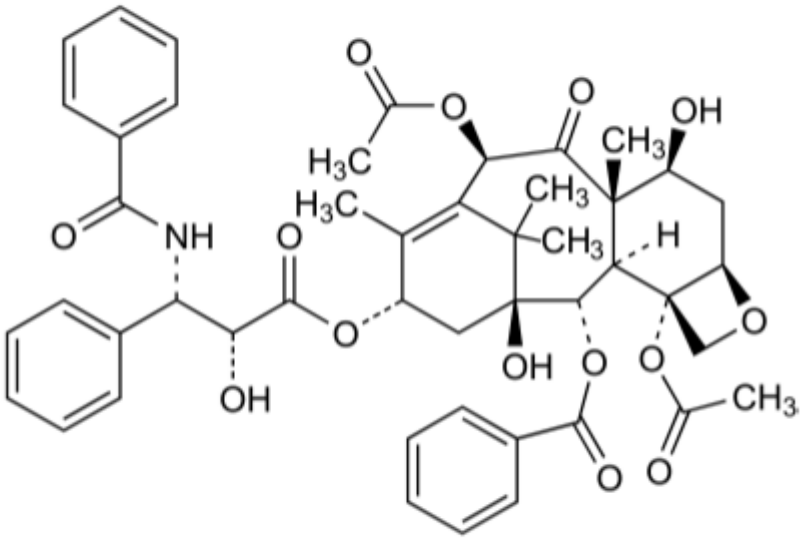
S 1 General Information

S 1.1 Nomenclature

Internationally used name	:	Paclitaxel
Chemical Name	:	Benzenepropanoic acid, b-(benzoylamino)- a-hydroxy-,6,12b bis(acetyloxy) -12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1 H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester, [2a R-[2aa,4b,4ab,6b,9a(aR* ,bS*),11a,12a,12aa,12ba]]-.(2aR,4 S,4a S,6 R,9 S,11 S,12 S,12a R,12b S)-1,2a,3,4,4a,6,9,10,11,12,12a,12b-Dodecahydro-4,6,9,11,12,12b-hexahydroxy-4a,8,13,13-tetramethyl-7,11-methano-5 H-cyclodeca[3,4]-benz[1,2- b]oxet-5-one 6,12b-diacetate, 12-benzoate, 9-ester with (2 R,3 S)- N-benzoyl-3-phenylisoserine.
Pharmacopoeial Name	:	Paclitaxel
Other Name	:	Paclitaxel; Taxol; Taxol A.
CAS Registry Number	:	33069-62-4
Laboratory Code	:	---
Pharmacopoeia	:	**United State Pharmacopoeia XXVII3**

S 1.2 Structure

PACLITAXEL USP



Molecular Formula	:	$C_{47}H_{51}NO_{14}$
Molecular Weight	:	853.91

S 1.3 General Properties

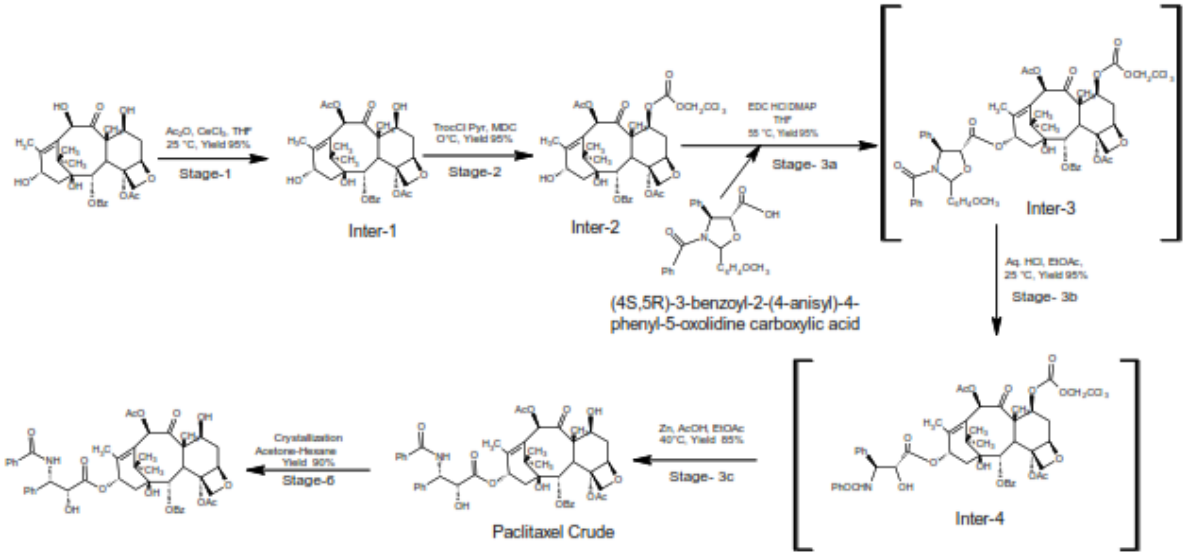
Appearance	:	White to off-white powder.
Solubility	:	Insoluble in water; soluble in alcohol.
Specific Optical Rotation	:	Between -49.0° and -55.0°
Microbial limits	:	The total aerobic microbial count does not exceed 100 cfu per g.
Bacterial endotoxins	:	It contains not more than 0.4 USP Endotoxin Unit per mg of paclitaxel.
Water	:	Not more than 4.0%
Residue on ignition	:	Not more than 0.2%.
Heavy Metals	:	0.002 %
Related Compounds	:	(i) Individual Impurity NMT 0.1 % (ii) Total Impurities NMT 2.0 %
Assay	:	97.0 % to 102.0 %.

S 2 Manufacture:

S 2.1 Manufacturer (s)

Site	Address	Responsibility
Administrative	**Sai Phytoceuticals Pvt. Ltd.,**S-553, Greater Kailash II New Delhi – 110048, India. Tel: 0091 11 29222188 Fax: 0091 11 29211855 Contact Person:- Anil G. Bhansali (Managing Director)	To arrange for raw materials, solvents, chemicals and engineering items required for production of bulk drug. To coordinate with plant and vendors for smooth operations of plant. To arrange for dispatch of goods at various places and exports.
Production	**Sai Phytoceuticals Pvt. Ltd.,** C-118 Industrial Area, Malanpur – 477117, Dist. Bhind, M.P, India. Tel: 0091 751 4010787 Mob: 0091 8889905588	Production, Purification and Packaging.
Analysis	Same as above	Analysis of raw material, finished products and In-process controls.
Contract manufacturing	Nil	----------
Other sites	Nil	----------

S 2.2 Descriptions of Manufacturing Process and Process Controls



S 2.3 Controls of Materials

10-Deacetyl Baccatin-III
Tetrahydrofuran
Acetic anhydride
Dichloromethane
Hexane
Methanol
Pyridine
2,2,2-Trichloroethyl chloroformate
Hydrochloric acid
Sodium bicarbonate
Sodium chloride
Sodium Sulphate
Toluene
(4S,5R)-3-Benzoyl-2-(4-methoxyphenyl)-4-Phenyl-5-oxazolidine carboxylic acid [Paclitaxel side chain]
4-Dimethyl Amino Pyridine
EDC Hcl
Ethyl acetate
Sodium dihydrogen phosphate dehydrate
Glacial acetic acid
Hyflow super cell
Zinc dust
Acetone
Process water

S 2.4 Controls of Critical Steps and Intermediates

Stage-1

Parameter P – 1 : - The temperature should be maintained during acetylation of the reaction mixture.

Limits **: -** 25ºC- 30 ºC

Stage-2

Parameter P – 2 **:-** The addition temperature of 2,2,2-Trichloroethyl chloroformate to be reaction mixture should be maintained.

Limits :- 0ºC- 5ºC

Stage-3

Parameter P – 3 **:-** After addition of Inter-2 paclitaxel side chain, EDC HCl and 4-DMEP in tetrahydrofuran reaction temperature should be maintained

Limits :- 60ºC- 65ºC

Stage-4

Parameter P - 4 **:-** Addition of HCl acid temperature should be maintained.

Limits :- 15ºC- 20ºC

Stage-5

Parameter P – 5 **:-** Time and temperature of the addition of acetic acid

Limits **:-** Time: 4 to 5 hrs. and Temperature: 30ºC- 40ºC

Stage-6

Parameter P – 6 :- Purification of Paclitaxel crude with acetone and hexane.

Limits :- Check assay by HPLC. Limit is 97.0 to 102. 0 %

S 2.5 Process Validations and/or Evaluation

It has been found from the above study that the process parameters do not deviate and are largely remaining unchanged after repeated batch processing at different times and using materials of different Quality.

The analysis results of the batches also justify the compliance of process parameters.

The assay of the active ingredient of the three batches does not deviate from the established limits.

In the opinion of the approving team the process stands validated in respect of the parameters considered during manufacturing.

S 2.6 Manufacturing Process Developments

The manufacturing Process was developed as per follows

A. Literature Survey:

All available Literatures such as Patents, Journal Articles, Research Papers, and Chemical Abstracts were thoroughly screened.

Process described under United States Patent number 5274137 and 5415869 was thoroughly studied for Paclitaxel further we develop the process for the preparation of Paclitaxel USP as per follows.

B. Initial Synthesis:

Laboratory Batches:

Laboratory batches (200 gm of Final Product) were taken using 500 ml Round Bottom Flask equipped with magnetic stirrer.

Following equipments were used for unit operations

Filtration: Nutsche Filter

Drying: Rotary Vacuum Dryer.

Q. A. dept. was fully involved to comply with cGMP, analytical testing and documentation as per FDA and EMEA requirements.

For R & D dept. highly motivated and experienced personnel were employed.

The method was duly validated after defining the critical process parameters.

The reaction mechanism, reaction pathway, unit operations, raw material balance, solvent recovery, quality of input raw materials, purification procedure, etc were fully understood.

The storage and packing of finial product was dully characterized.

The finished product was duly characterized against reference standard.

Accelerated stability studies were performed in a package similar to proper commercial package.

C. Scale Up to 2.0 Kg.

The process was scaled up to **2.0 Kg** using assembly of larger capacity **e. g.:** Glass Reactor with Stirrer, Centrifuge, Nutsche Filter, and Tray Dryers.

Critical process parameters for scaled up process were duly revised to get consistent quality and yield.

Process validation was performed on the first three batches after establishing Equipment and Raw Materials suitability.

Stability studies at Storage Temperature and Accelerated Stability studies were conducted.

S 3 Characterization

S 3.1 Elucidation of Structure and Other Characteristics

The results and corresponding to the spectral data indicates the confirmation of molecule structure of Paclitaxel.

S 3.2 Impurities

The impurities present in Paclitaxel can be broadly classified under potential impurities.

1. Potential Impurities from the route of the synthesis adopted.

Potential impurities that can be present are mentioned in the USP

Impurity

10-Deacetyl baccatin III

Baccatin III

Photodegradant

10-Deacetylpaclitaxel

2-Debenzoylpaclitaxel 2-pentenoate

Oxetane ring opened, acetyl and benzoyl

10-Acetoacetyl paclitaxel

10-Deacetyl-7epipaclitaxel (Paclitaxel related compound B)

7-Epipaclitaxel

10,13Bissidechainpaclitaxel

7-Acetyl paclitaxel

13-Tes-baccatin III

7-Tes-paclitaxel

Any other single impurity

Total impurities

S 4 Control of Drug Substance

S 4.1 Specifications

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SPECIFICATION	STP NUMBER: SPPL/QC/SPEC/PCT-USP/12
	SECTION: QUALITY CONTROL

PRODUCT	Paclitaxel-USP			
ISSUE DATE	10/01/2022	REVIEW DATE	10/01/2024	Page 1 of 2
EFFECTIVE DATE	10/01/2022	SUPERSEDES	05	

S. No.	Tests	Limits
01.	**Description**	White or almost white crystalline powder
02.	**Identification** **By IR** **By HPLC**	 Matches with the reference standard. The retention time of the major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation, as obtained in the Assay.
03.	**Specific optical rotation (On anhydrous and solvent free basis (°)**	-49 to -55.0
04.	**Water by KF (% w/w)**	NM T 4.0
05.	**Residue on Ignition (% w/w)**	NMT 0.2
06.	**Heavy metals (% w/w)**	NMT 0.002
07.	**Related compounds (By HPLC) (%)**	
	10-Deacetylbaccatin III	NMT 0.1
	Baccatin III	NMT 0.2
	Photodegradant	NMT 0.1
	10-Deacetylpaclitaxel	NMT 0.5
	2-Debenzoylpaclitaxel-2-pentenoate	NMT 0.7
	Oxetane ring opened, acetyl and benzoyl	X_1
	10-Acetoacetylpaclitaxel	X_2
	10-Deacetyl-7- epipaclitaxel (paclitaxel related compound B)	X_3
	7-Epipaclitaxel	NMT 0.4
	10,13-Bissidechainpaclitaxel	NMT 0.5
	7-Acetylpaclitaxel	NMT 0.6%
	13-Tes-baccatin III	NMT 0.1%
	7-Tes-paclitaxel	NMT 0.3%
	Any other single impurity	NMT 0.1%
	Total Impurities	NMT 2.0%
	*** Sum of X_1, X_2 and X_3 should not be more than 0.4%**	

Prepared by : QC Chemist	Checked by : QC Manager	Approved by : QA Manager
Sign. :	Sign. :	Sign. :
Date : 10/01/2022	Date :	Date : 10/01/2022

QUALITY CONTROL DEPARTMENT APPROVED 10/01/2022

QUALITY ASSURANCE DEPARTMENT

Sai Phytoceuticals (P) Ltd. Address: C-128 Industriaharca Malanpur Dist.-Bhind (M.P.)

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SAI PHYTOCEUTICALS (P) LTD.

RESTRICTED CIRCULATION
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SPECIFICATION			STP NUMBER: SPPL/QC/SPEC/PCT-USP/12 SECTION: QUALITY CONTROL	
PRODUCT	**Paclitaxel-USP**			
ISSUE DATE	**10/01/2022**	**REVIEW DATE**	**10/01/2024**	Page 2 of 2
EFFECTIVE DATE	**10/01/2022**	**SUPERSEDES**	**05**	

08.	**Residual Solvents (ppm)**	
	Dichloromethane	NMT 600 ppm
	Hexane	NMT 290 ppm
	Tetrahydrofuran	NMT 720 ppm
	Ethyl acetate	NMT 5000 ppm
	Acetone	NMT 5000 ppm
	Pyridine	NMT 200 ppm
	Acetic Acid	NMT 5000 ppm
	Methanol	NMT 3000 ppm
09.	**Microbial Limit**	
	The total aerobic microbial count (cfu/g)	NMT 100
	Staphylococcus aureus	Absent.
	Pseudomonas aeruginosa.	Absent
	Salmonella species.	Absent.
	Escherichia coli	Absent.
10.	**Bacterial Endotoxins Test (USP endotoxin unit/mg)**	NMT 0.4
11.	**Assay (By HPLC) (On anhydrous and solvent free basis) (% w/w)**	97.0 to 102.0

Prepared by : QC Chemist	Checked by : QC Manager	Approved by : QA Manager
Sign. :	Sign. :	Sign. :
Date : 10/01/2022	Date : 10/01/2022	Date : 10/01/2022

QUALITY CONTROL DEPARTMENT APPROVED

QUALITY ASSURANCE DEPARTMENT APPROVED

Sai Phytoceuticals (P) Ltd. Address: C-213 Industrial area Mahanpur Dist.-Bhind (M.P.)

S 4.2 Analytical Procedures

Paclitaxel analyzed as per 'USP' test procedures. Such test procedures apply to both product release and stability studies.

S 4.3 Validation of Analytical Procedure

The specifications of the Paclitaxel are as per United State Pharmacopoeia XXVII

Method of Analysis for Assay: High Performance Liquid Chromatography

The method followed by us exactly same as detailed in United State Pharmacopoeia XXVII. Since the method is Pharmacopoeial and we have followed without any alteration, validation for the same is not discussed here.

S 4.4 Batch Analysis

Commercial batches of Paclitaxel were analysed in the Quality Control Laboratory of Sai Phytoceuticals as per the specification and analytical procedure.

Batch No.	Manufacturing Site	Manufacturing Date
PCT-17001	Sai Phytoceuticals	Feb 2017
PCT-17002		Feb 2017
PCT-17003		Feb 2017

Test	Specifications	Observations		
		Batch no. PCT-17001	**Batch no.** PCT-17002	**Batch no.** PCT-17003
Description	A White to almost white power.	White powder	White powder	White powder
Identification				
1. By IR	1. IR Spectrum of sample matches with the Paclitaxel RS.	Complies	Complies	Complies
2. By HPLC	2. The retention time of the major peak of the sample solution corresponds to that of the standard solution, as obtained in the Assay.	Complies	Complies	Complies
Water By KF	NMT 4.0%	1.06%	1.10%	0.58%
Specific Optical Rotation (on anhydrous and	- 49° to -55°	- 50.50	- 50.5	- 52.1

solvent free basis)				
Residue on Ignition	NMT 0.2%	0.08%	0.06%	0.07%
Heavy metals	NMT 20ppm	Less than 20ppm	Less than 20ppm	Less than 20ppm
Related Substances (As Per USP Related Compounds Test 2)				
1. 10-Deacetylbaccatin III. 2. Baccatin III 3. Photodegradant. 4. 10-Deacetylpaclitaxel. 5. 2-Debenzoylpaclitaxel-2-pentenoate. 6. Oxetane ring opened acetyl and benzoyl 7. 10-Acetoacetylpaclitaxel. 8. 10-Deacetyl-7-epipaclitaxel 9. 7-Epipaclitaxel 10. 10,13-Bissidechainpaclitaxel. 11. 7-Acetylpaclitaxel 12. 13-Tes-baccatin III. 13. 7- Tes-paclitaxel. 14. Any other single impurity 15. Total impurities	1. NMT 0.1% 2. NMT 0.2% 3. NMT 0.1% 4. NMT 0.5% 5. NMT 0.7% 6+7+8 = NMT 0.4% 9. NMT 0.4% 10. NMT 0.5% 11. NMT 0.6% 12. NMT 0.1% 13. NMT 0.3% 14. NMT 0.1% 15. NMT 2.0%	1.Not detected. 2.Not detected. 3.Not detected. 4.Not detected 5.Not Detected 6+7+8= Not detected 9.Not detected 10.Not detected 11. Not detected 12. Not Detected 13. Not detected 14. 0.08% 15.0.15%	1.Not detected. 2.Not detected. 3.Not detected. 4.Not detected 5.Not Detected 6+7+8= Not detected 9.Not detected 10.Not detected 11. Not detected 12. Not Detected 13. Not detected 14. 0.07% 15.0.18%	1.Not detected. 2.Not detected. 3.Not detected. 4.Not detected 5.Not Detected 6+7+8= Not detected 9.Not detected 10.Not detected 11. Not detected 12. Not Detected 13. Not detected 14. 0.06% 15.0.14%
Residual solvent 1. Dichloromethane 2. Hexane 3. Tetrahydrofuran 4. Ethyl acetate 5. Acetone 6. Pyridine 7. Acetic Acid	 1. NMT 600 ppm 2. NMT 290 ppm 3. NMT 720ppm 4. NMT 5000ppm 5. NMT 5000ppm 6. NMT 200ppm 7. NMT 5000ppm	 1. 92 ppm 2. 92 ppm 3. ND 4. ND 5. 2115 ppm 6. ND 7. ND	 1. 92 ppm 2. 102 ppm 3. ND 4. ND 5. 2115 ppm 6. ND 7. ND	 1. 92 ppm 2. 102 ppm 3. ND 4. ND 5. 2115 ppm 6. ND 7. ND
Microbial Test 1. Total aerobic microbial count. 2. Staphylococcus aureus 3. Pseudomonas aeruginosa 4. Salmonella species 5. Escherichia coli	 1.NMT 100cfu/g 2. Absent 3. Absent 4. Absent 5. Absent	 1. 10cfu/g 2. Absent 3. Absent 4. Absent 5. Absent	 1. 10cfu/g 2. Absent 3. Absent 4. Absent 5. Absent	 1. 10cfu/g 2. Absent 3. Absent 4. Absent 5. Absent
Bacterial Endotoxins Test	NMT 0.4 USP Endotoxin unit/mg	less than 0.4	less than 0.4	less than 0.4
Assay by HPLC (On anhydrous and solvent free basis)	97.0% to 102.0%	99.65%	99.86%	98.3%

S 4.5 Justifications of Specifications

General Specifications:

Proposed: As per United State Pharmacopoeia XXVII

Justifications: Acceptable by Regulatory Authorities.

Characters: Description and Solubility

After purification the appearance of final product is studied for various batches the limit is set in United State Pharmacopoeia XXVII and same is set by us.

Solubility is carried out in different solvents for different concentrations and limit is set in United State Pharmacopoeia XXVII and same is set by us.

Identification:

A. IR spectrum shall match with the IR of Reference Standard.

C. The retention time of the major peak in the chromatogram of Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the

Assay

Specific Rotation:

We have proposed specific rotation of the drug: Between -49.0° and -55.0° at 20°

The same is the limit set by United State Pharmacopoeia XXVII

Microbial Limits:

We have proposed the total aerobic microbial count does not exceed 100 cfu per g. It meets the requirements of the tests for the absence of Staphylococcus aureus, Pseudomonas aeruginosa, Salmonella species, and Escherichia coli.

The same is the limit set by United State Pharmacopoeia XXVII

Bacterial Endotoxin:

We have proposed bacterial endotoxin content of the drug: not more than 0.4 USP Endotoxin Unit per mg.

The same is the limit set by United State Pharmacopoeia XXVII

Water:

We have proposed the water contents of the drug Not more than 4.0 %

The same is the limit set by United State Pharmacopoeia XXVII

Residue on Ignition:

We have proposed the residue on ignition not more than 0.2 %

The same is the limit set by United State Pharmacopoeia XXVII

Heavy Metals:

We have proposed limit of heavy metal as not more than 0.002 %

The same is the limit set by United State Pharmacopoeia XXVII

Related Substances:

The synthetic procedure used for manufacturing Paclitaxel USP is same as that followed by the originator.

There are only minor modifications in the quantities and solvents to achieve the better yield and quality. The Potential impurities in United State Pharmacopoeia XXVII are mentioned in detailed.

Assay:

We have proposed Assay of the drug: 97.0 % to 102.0 %.

The same is the limit set by United State Pharmacopoeia XXVII

S 5 Reference Standard or Materials

Reference Standard:

Paclitaxel WS is used as the Primary Working Standard.

It has traceability to specifications set as per United State Pharmacopoeia XXVII

Date of preparation and Standardization **:** --/--/----

Validity of usage **:** --/--/----

Working Standard Number **:** PCT-17000 W.S

Evaluation with **:** Paclitaxel RS

For all practical purpose Working Standard prepared In-House is used.

Elemental analysis, IR, MASS and studies confirm the structural similarity of the material.

Working standard is preserved in tight, light-resistant containers.

S 6 Container Closure System

Paclitaxel is packed in clean double lined L.D.P.E Bags of capacity 0.500 Kg and 1.000 kg and 2.00 Kg pack.

The packed material is flushed with nitrogen, sealed and then packed in Triple Laminated Aluminium Pouch and finally kept in HDPE Drum.

These drums are securely strapped and sealed with Tamperproof Metal seals and labeled on the body and top of the lid.

The labels give details such as:

1. Name of the Product
2. Manufacturing license Number
3. Batch number with manufacturing and expiry dates
4. Quantity of the material packed
5. Name and address of the company

If the material packed in drum is compacted, then the drum is labeled accordingly.

The labels are checked regularly for colour shade, printed matter and size to maintain the consistency.

The L.D.P.E. bags and Aluminum drums are also regularly checked for quality.

The specifications are given on the following pages.

Accelerated stability studies at **40°C ±2°C and 75%± 5%** relative humidity have been conducted on the material packed in polythene bags similar to the commercial pack.

The satisfactory results indicate that Paclitaxel packed in polythene bags is stable and that there was no permeation of moisture through the polythene bags.

Further there are no customer complaints regarding any kind of spillage of the material due to torn polythene bags.

The Aluminium drums containing the material packed in L.D.P.E. bags are also not damaged during the transport and the material packed inside is intact.

The sticker-type labels fixed on the drums are legible and clear furnishing the necessary details about the material packed inside the drum.

In addition the Tamperproof seals on the packed drums eliminate any chances of contamination of the product during the transport.

Thus, precautions are duly taken to maintain the integrity of the product by using appropriate and good quality packaging materials.

S 7 Stability

S 7.1 Stability Summary and Conclusion

The following stability studies program is adopted by Sai Phytoceuticals Pvt. Ltd for checking the stability of Paclitaxel.

1. STABILITY STUDIES AT STORAGE TEMPERATURE:

The bulk drug was packed in a container similar to the commercial pack, kept at storage temperature (**25°C±2°C / RH 60 % ±5 %**).

It is tested at intervals of three months of the first year and later on once in six months up to thirty six months.

Thus, three batches of Paclitaxel USP Manufactured by Sai Phytoceuticals Pvt. Ltd (B.No. PCT-17001, PCT-17002, PCT-17003) were subjected to stability testing at storage temperature.

2. ACCELERATED STABILITY STUDIES:

Same three commercial batches of Paclitaxel USP manufactured by Sai Phytoceuticals Pvt. Ltd (B.No. PCT17001, PCT-17002, PCT-17003) were also subjected to accelerated stability studies at **40°C ±2°C / RH 75%±5%** for three months and six months.

S 7.2 Post-approval Stability Protocol and Stability Commitment

After approval of the product following stability studies will be performed:

Every six months, one batch from commercial production will be subjected to stability studies at Room Temperature till the expiry of the product.

The protocol for the same will be same as that described above for the initial batches.

Further, If there are any process modifications then first three batches manufactured by the modified process are subjected to the stability program as given above.

S 7.3 Stability Data

Refer to stability data in Module 3

Drug Product

P 1 Description and Composition of the Drug Product

Description

A clear colourless to slight yellow viscous solution packed in 50 ml USP type I amber color glass vial.

Composition

Brand Name : Paclimed 300mg

Generic Name : Paclitaxel injection USP 300mg/50ml

Label Claim :

Each ml Contains:

Paclitaxel USP----6mg

For per unit:

S.no	Name of the ingredients	Specification	Label Claim (mg)	Overages	Quantity per Unit / mg	Function
1	Paclitaxel	USP	300 mg	NA	300 mg*	Anticancer
2	Polyoxyl 35 castor Oil	USP	---	NA	26.350 gm	Solvent
3	Citric Acid	USP	----	NA	100 mg	Tonicity agent
4	Dehydrated Alcohol	USP	----	NA	Q.s. to 30.00 gm	Solvent

For batches

S.no	Name of the ingredients	Specification	Label Claim (mg)	Quantity per Unit / mg	Quantity per batch kg (1000 vials)	Function
1	Paclitaxel	USP	300 mg	300 mg*	0.300 kg	Anticancer
2	Polyoxyl 35 castor Oil	USP	---	26.350 gm	26.350 kg	Solvent
3	Citric Acid	USP	----	100 mg	0.100 kg	Tonicity agent
4	Dehydrated Alcohol	USP	----	Q.s. to 30.00 gm	Q.s. to 30 kg	Solvent

* Actual quantity of Paclitaxel is based on QC result.

ABBREVIATIONS

USP: United State Pharmacopoeia

P 2 Pharmaceutical Development

The development of Paclitaxel injection USP 300mg/50ml is carried out on the basis of physicochemical properties of molecule; it is decided to choose accordingly the suitability and compatibility.

P 2.1 COMPONENTS OF DRUG PRODUCT

P 2.1.1 ACTIVE INGREDIENT

COMPATIBILITY OF THE API (S) WITH EXCIPIENTS:

Choice of Excipients

The excipients were chosen for formulating Paclitaxel injection USP 300mg/50ml been widely used in injectable pharmaceutical formulations. To make a successful injection formulation each excipient was analyzed for its suitability with Paclitaxel.

Based on the compatibility study and literature, the following excipients are selected for formulation development.

Sr. No.	Excipients	Specifications or Reference	Function
1	Polyoxyl 35 castor Oil	USP	Solvent
2	Citric Acid	USP	Tonicity agent
3	Dehydrated Alcohol	USP	Solvent

Compatibility of drug substance with the drug substances Pre-formulation studies conducted to check Compatibility of various API with excipients. Drug and Excipients were taken in 1:1 molar ratio and properly mixed and filled in hermetically sealed glass vials kept at Accelerated Condition (40ºC/75%RH) for one month to check physical changes i.e. Appearance and color.

Sr. No	Drug Substance	Excipients	Observation
1	Paclitaxel	Polyoxyl 35 castor Oil	No significant change is observed
2	Paclitaxel	Citric Acid	No significant change is observed
3	Paclitaxel	Dehydrated Alcohol	No significant change is observed

P 2.1.2 Excipients

Different excipients are included in the dosage form along with the active ingredient. The excipients for the compatibility study have been selected based on following considerations.

1. Polyoxyl 35 castor Oil

Function: Emulsifying agent; solubilizing agent; wetting agent.

Polyoxyethylene castor oil derivatives are nonionic solubilizers and emulsifying agents used in oral, topical, and parenteral pharmaceutical formulations. Polyoxyl 35 castor oil is mainly used as an emulsifing and solubilizing agent, and is particularly suitable for the production of aqueous liquid preparations containing volatile oils, fat-soluble vitamins, and other hydrophobic substances.

2. Citric Acid

Function: Acidifying agent; antioxidant; buffering agent; chelating agent; flavor enhancer; preservative.

Citric acid (as either the monohydrate or anhydrous material) is widely used in pharmaceutical formulations and food products, primarily to adjust the pH of solutions. It has also been used experimentally to adjust the pH of tablet matrices in enteric-coated formulations for colon-specific drug delivery. Citric acid monohydrate is used in the preparation of effervescent granules, while anhydrous citric acid is widely used in the preparation of effervescent tablets.

3. Dehydrated Alcohol

Function: Antimicrobial preservative; disinfectant; skin penetrant; solvent.

Although ethanol is primarily used as a solvent, it is also employed as a disinfectant, and in solutions as an antimicrobial preservative.

P 2.2 Finished Product

P 2.2.1 Formulation Development

Development of Paclitaxel injection USP 300mg/50ml planned by considering Dr. Reddy's, Mitotax-300 (reference product) as reference. Based on literature of API, innovator dosage form details and pre-formulation data, developmental process was selected.

The formulation development of Paclitaxel injection USP 300mg/50ml was designed by evaluating the following critical attributes.

2.2.1.1 Reference Product Characterization

2.2.1.2 Selection of the Drug Substance

2.2.1.3 Drug & Excipients Compatibility Studies (Excipients Selection)

2.2.1.4 Formula Optimization

Formula optimization:

Trial 01

Trial 1				**Batch Size: 100 Vials**
Sr. No.	**Ingredients**	**Specifications Or Reference**	**Quantity per Unit / mg**	**Function**
1	Paclitaxel	USP	300 mg*	Anticancer
2	Polyoxyl 35 castor Oil	USP	26.350 gm	Solvent
3	Citric Acid	USP	100 mg	Tonicity agent
4	Dehydrated Alcohol	USP	Q.s. to 30.00 gm	Solvent

*This quantity is based on assay & water content

Certificate of Analysis		
Product Name	Paclitaxel injection USP 300mg/50ml	
Batch No:	RDI19085	
Packing	50 ml USP type I amber color glass vial with rubber stopper and flip-off aluminium seal.	
Tests	**Limits**	**Result**
Description	A clear colourless to slight yellow viscous solution packed in 50 ml USP type I amber color glass vial.	A clear colourless viscous solution packed in 50 ml USP type I amber color glass vial.
Identification A. B.	The retention time of the major peak in the chromatogram of the test solution corresponds to that in the chromatogram of the standard solution, as obtained in test for limit of degradation products. The retention time of the major peak in the chromatogram of the test solution corresponds to that in the chromatogram of the standard solution, as obtained in test for limit of Assay.	Complies Complies
Extractable volume	The volume should not less than the nominal volume.	50.1 ml
pH	3.0 to 7.0	4.980

Particulate matter Visual particulate Sub-visible particles	Injection should be clear and practically free from particles that can be observed on visual inspection by the unaided eye. The average number of particles present in the units tested does not exceed 6000 per container equal to or greater than 10µm and does not exceeds 600 per container equal to or greater than 25µm.	Complies Complies
Limit of degradation products: Baccatin III at RRT 0.19 Ethyl ester side chain at RRT 0.21 10-Deacetylpaclitaxel 10-Deacetyl-7-epipaclitaxel (Paclitaxel related compound B) 7-Epipaclitaxel Any other Paclitaxel degradation product Total Paclitaxel degradation product	 NMT 0.8% NMT 0.4% NMT 0.8% NMT 0.5% NMT 0.6% NMT 0.1% NMT 2.0%	 ND ND ND ND ND 0.004% 0.08%
Bacterial Endotoxin	Not more than 0.67 USP Endotoxin Unit per mg of Paclitaxel.	Less than 0.67 USP Endotoxin Unit per mg
Sterility	Shall comply for sterility	Complies
Assay Each ml Contains: Paclitaxel USP---- 6mg	Not less than 5.4 mg and not more than 6.6 mg. (NLT 90% and NMT 110%).	5.985mg (99.76%)

Conclusion: From the above results and observations, batch complies all the test parameters.

Trial 02

Trial 2				**Batch Size: 100 Vials**
Sr. No.	**Ingredients**	**Specifications Or Reference**	**Quantity per Unit / mg**	**Function**
1	Paclitaxel	USP	300 mg*	Anticancer
2	Polyoxyl 35 castor Oil	USP	26.350 gm	Solvent
3	Citric Acid	USP	100 mg	Tonicity agent
4	Dehydrated Alcohol	USP	Q.s. to 30.00 gm	Solvent

*This quantity is based on assay & water content

Certificate of Analysis		
Product Name	Paclitaxel injection USP 300mg/50ml	
Batch No:	RDI19086	
Packing	50 ml USP type I amber color glass vial with rubber stopper and flip-off aluminium seal.	
Tests	**Limits**	**Result**
Description	A clear colourless to slight yellow viscous solution packed in 50 ml USP type I amber color glass vial.	A clear colourless viscous solution packed in 50 ml USP type I amber color glass vial.
Identification A. B.	The retention time of the major peak in the chromatogram of the test solution corresponds to that in the chromatogram of the standard solution, as obtained in test for limit of degradation products. The retention time of the major peak in the chromatogram of the test solution corresponds to that in the chromatogram of the standard solution, as obtained in test for limit of Assay.	Complies Complies
Extractable volume	The volume should not less than the nominal volume.	50.1 ml
pH	3.0 to 7.0	4.982
Particulate matter Visual particulate Sub-visible particles	Injection should be clear and practically free from particles that can be observed on visual inspection by the unaided eye. The average number of particles present in the units tested does not exceed 6000 per container equal to or greater than 10µm and does not exceeds 600 per container equal to or greater than 25µm.	Complies Complies
Limit of degradation products:		
Baccatin III at RRT 0.19	NMT 0.8%	ND
Ethyl ester side chain at RRT 0.21	NMT 0.4%	ND
10-Deacetylpaclitaxel	NMT 0.8%	ND
10-Deacetyl-7-epipaclitaxel (Paclitaxel related compound B)	NMT 0.5%	ND
7-Epipaclitaxel	NMT 0.6%	ND
Any other Paclitaxel degradation product	NMT 0.1%	0.005%
Total Paclitaxel degradation product	NMT 2.0%	0.09%
Bacterial Endotoxin	Not more than 0.67 USP Endotoxin Unit per mg of Paclitaxel.	Less than 0.67 USP Endotoxin Unit per mg

Sterility	Shall comply for sterility	Complies
Assay Each ml Contains: Paclitaxel USP---- 6mg	Not less than 5.4 mg and not more than 6.6 mg. (NLT 90% and NMT 110%).	5.987mg (99.79%)

Conclusion: From the above results and observations, batch complies all the test parameters.

Trial 03

Trial 3				**Batch Size: 100 Vials**
Sr. No.	**Ingredients**	**Specifications Or Reference**	**Quantity per Unit / mg**	**Function**
1	Paclitaxel	USP	300 mg*	Anticancer
2	Polyoxyl 35 castor Oil	USP	26.350 gm	Solvent
3	Citric Acid	USP	100 mg	Tonicity agent
4	Dehydrated Alcohol	USP	Q.s. to 30.00 gm	Solvent

*This quantity is based on assay & water content

Certificate of Analysis		
Product Name	Paclitaxel injection USP 300mg/50ml	
Batch No:	RDI19087	
Packing	50 ml USP type I amber color glass vial with rubber stopper and flip-off aluminium seal.	
Tests	**Limits**	**Result**
Description	A clear colourless to slight yellow viscous solution packed in 50 ml USP type I amber color glass vial.	A clear colourless viscous solution packed in 50 ml USP type I amber color glass vial.
Identification A.	The retention time of the major peak in the chromatogram of the test solution corresponds to that in the chromatogram of the standard solution, as obtained in test for limit of degradation products.	Complies
B.	The retention time of the major peak in the chromatogram of the test solution corresponds to that in the chromatogram of the standard solution, as obtained in test for	Complies

	limit of Assay.	
Extractable volume	The volume should not less than the nominal volume.	50.1 ml
pH	3.0 to 7.0	4.971
Particulate matter Visual particulate Sub-visible particles	 Injection should be clear and practically free from particles that can be observed on visual inspection by the unaided eye. The average number of particles present in the units tested does not exceed 6000 per container equal to or greater than 10µm and does not exceeds 600 per container equal to or greater than 25µm.	 Complies Complies
Limit of degradation products: Baccatin III at RRT 0.19 Ethyl ester side chain at RRT 0.21 10-Deacetylpaclitaxel 10-Deacetyl-7-epipaclitaxel (Paclitaxel related compound B) 7-Epipaclitaxel Any other Paclitaxel degradation product Total Paclitaxel degradation product	 NMT 0.8% NMT 0.4% NMT 0.8% NMT 0.5% NMT 0.6% NMT 0.1% NMT 2.0%	 ND ND ND ND ND 0.005% 0.12%
Bacterial Endotoxin	Not more than 0.67 USP Endotoxin Unit per mg of Paclitaxel.	Less than 0.67 USP Endotoxin Unit per mg
Sterility	Shall comply for sterility	Complies
Assay Each ml Contains: Paclitaxel USP----6mg	 Not less than 5.4 mg and not more than 6.6 mg. (NLT 90% and NMT 110%).	 5.991mg (99.85%)

Conclusion: According to the above data, the trial batches have reproducibility and hence we proceed for the scale up process.

Trial 4

Scale-Up / Process Optimization Studies:

Based on prototype formulation of development batches the following formula and the process was proposed for Scale – up studies of Paclitaxel injection USP 300mg/50ml. The composition of scale-up batch was presented below.

Batch No. RDI19087

UNIT FORMULA:

Trial 4				**Batch Size: 100 Vials**
Sr. No.	**Ingredients**	**Specifications Or Reference**	**Quantity per Unit / mg**	**Function**
1	Paclitaxel	USP	300 mg*	Anticancer
2	Polyoxyl 35 castor Oil	USP	26.350 gm	Solvent
3	Citric Acid	USP	100 mg	Tonicity agent
4	Dehydrated Alcohol	USP	Q.s. to 30.00 gm	Solvent

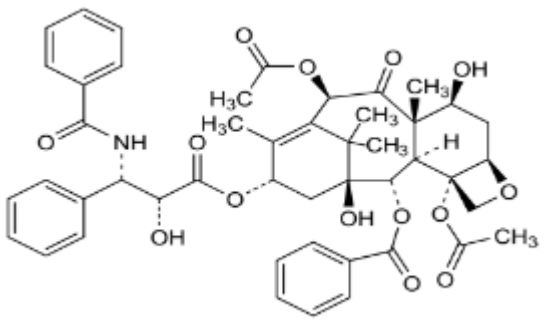
*This quantity is based on assay & water content

P 2.2.2 Overages

No overages**.**

P 2.2.3 Physiochemical and Biological Properties

Paclitaxel

Appearance	White to off-white powder.
Solubility	Insoluble in water; soluble in alcohol.
CAS No.	33069-62-4
Structural Formula	
Molecular Formula	$C_{47}H_{51}NO_{14}$
Molecular Mass	853.91

P 2.3 Manufacturing Development

1.1 Decartoning of vials.

1.2 Inspection of Vials.

1.3 Washing and De-pyrogenation of vials.

1.4 Washing, Siliconization, Sterilization and drying of rubber plugs.

1.5 Autoclaving of seals.

1.6 Washing and Sterilization of Machine Parts.

1.7 Weighing & verification of quantity of raw material & transfer to filling area

1.8 Preparation of Bulk Solution

1.9 Vial Filling and Stoppering

1.10 Vial Sealing

1.11 Visual Inspection.

1.12 In process Quality Control Checks

1.13 Labeling & Packaging.

P 2.4 Container closure System

The development of container closure system for Paclitaxel injection USP 300mg/50ml, includes following parameters to study-

Accelerated Stability Data				
Product Name	Paclitaxel injection USP 300mg/50ml	**Storage**	40 ± 2°C & 75 ± 5% RH	
Batch No:	RDI19087			
Packing	50 ml USP type I amber color glass vial with rubber stopper and flip-off aluminium seal. Such 1 labeled vial is packed in printed carton along with pack insert.			
Tests	**Limits**	**Initial**	**3 M**	**6 M**
Description	A clear colourless to slight yellow viscous solution packed in 50 ml USP type I glass vial.	A clear colourless viscous solution packed in 50 ml USP type I glass vial.	A clear colourless viscous solution packed in 50 ml USP type I glass vial.	A clear colourless viscous solution packed in 50 ml USP type I glass vial.
Identification A)	The retention time of the major peak in the chromatogram of the test solution corresponds to that in the chromatogram of the standard solution, as	Complies	Complies	Complies

B)	obtained in test for limit of degradation products. The retention time of the major peak in the chromatogram of the test solution corresponds to that in the chromatogram of the standard as obtained in test for limit of assay.	Complies	Complies	Complies
Extractable volume	The volume should not less than the nominal volume.	50.1 ml	50.1 ml	50.1 ml
pH	3.0 to 7.0	4.971	4.968	4.962
Particulate matter A) Visual particles	Injection should be clear and practically free from particles that can be observed on visual inspection by the unaided eye.	Complies	Complies	Complies
B) Sub- visible Particles	The average number of particles present in the units tested does not exceed 6000 per container equal to or greater than 10µm and does not exceeds 600 per container equal to or greater than 25µm.	Complies	Complies	Complies
Limit of degradation products:				
Baccatin III at RRT 0.19	NMT 0.8%	ND	ND	ND
Ethyl ester side chain at RRT 0.21	NMT 0.4%	ND	ND	ND
10-Deacetylpaclitaxel	NMT 0.8%	ND	ND	ND
10-Deacetyl-7-epipaclitaxel (Paclitaxel related compound B)	NMT 0.5%	ND	ND	ND
7-Epipaclitaxel	NMT 0.6%	ND	ND	ND
Any other Paclitaxel degradation product	NMT 0.1%	0.005%	0.005%	0.008%
Total Paclitaxel degradation product	NMT 2.0%	0.12%	0.14%	0.18%
Sterility	Shall comply for Sterility	Complies	Complies	Complies
Bacterial Endotoxin	Not more than 0.67 Endotoxin Unit per mg	Complies	Complies	Complies

	of Paclitaxel.			
Assay: Each ml Contains: Paclitaxel USP – 6 mg	NLT 5.4 mg and NMT 6.6 mg (NLT 90% and NMT 110%)	5.991mg (99.85%)	5.988 mg (99.80%)	5.983 mg (99.73%)

Paclitaxel injection USP 300mg/50ml packs similar to the commercial pack were kept for accelerated stability studies at temperature (40°C ± 2°C/RH 75 % ± 5 %) respectively. During this time period significant changes in physical and chemical stabilities were not observed. Since accelerated data shows no change over time, this explains about compatibility between primary package and the finished product.

P 2.6 Microbiological Attributes

Sr No.	Pathogens	Limit	Report
1.	Bacterial Endotoxin Test	Not more than 0.67 USP Endotoxin Unit per mg of Paclitaxel.	0.67 USP Endotoxin Unit per mg of Paclitaxel.
2.	Sterility	Shall comply for sterility	Complies
3.	Particulate Matter	≥10µm (NMT 6000 particles/container)	Complies
		≥25µm (NMT 600 particles/container)	Complies

P 2.7 Compatibility

Paclitaxel injection USP should not be mixed in the same syringe with any drug.

P 3 Manufacture

3.1 Manufacturer

Manufacturing Facility	Responsibility
Cosmas Research Lab Limited Village Gaunspura P.O. Noorpur Bet Hambran, Ludhiana - 141008 (Punjab) INDIA	Production, packaging, labelling, testing, storage and release
Manufactured for or Marketing Authorization holder Address	**Intermed Laboratories Private Limited** New no: 17, Old NO.4,G.K. Industrial Estate, Arcot Road & No.19, Alapakkam Main Road, Porur, Chennai - 600 116. India

P 3.2 Batch Formula

Qualitative & Quantitative Formula

For per unit:

S.no	Name of the ingredients	Specification	Label Claim (mg)	Overages	Quantity per Unit / mg	Function
1	Paclitaxel	USP	300 mg	NA	300 mg*	Anticancer
2	Polyoxyl 35 castor Oil	USP	---	NA	26.350 gm	Solvent
3	Citric Acid	USP	----	NA	100 mg	Tonicity agent
4	Dehydrated Alcohol	USP	----	NA	Q.s. to 30.00 gm	Solvent

For batches

S.no	Name of the ingredients	Specification	Label Claim (mg)	Quantity per Unit / mg	Quantity per batch kg (1000 vials)	Function
1	Paclitaxel	USP	300 mg	300 mg*	0.300 kg	Anticancer
2	Polyoxyl 35 castor Oil	USP	---	26.350 gm	26.350 kg	Solvent
3	Citric Acid	USP	----	100 mg	0.100 kg	Tonicity agent
4	Dehydrated Alcohol	USP	----	Q.s. to 30.00 gm	Q.s. to 30 kg	Solvent

* Actual quantity of Paclitaxel is based on QC result.

ABBREVIATIONS

USP: United State Pharmacopoeia

P 3.3 Description of manufacturing process and process controls

The details of manufacturing process of Paclitaxel injection USP 300mg/50ml along with the list of Equipment utilized in the manufacturing process are presented as follows:

1. List of Equipment
2. Flow diagram of the manufacturing process
3. Narrative description of the manufacturing process

All operating conditions correspond to the currently valid GMP-regulations.

All the critical areas are equipped with the appropriate air, treatment and circulation, systems so that cross-contamination is avoided.

Only well trained personnel should enter and being occupied within the areas and for the preparation of the product.

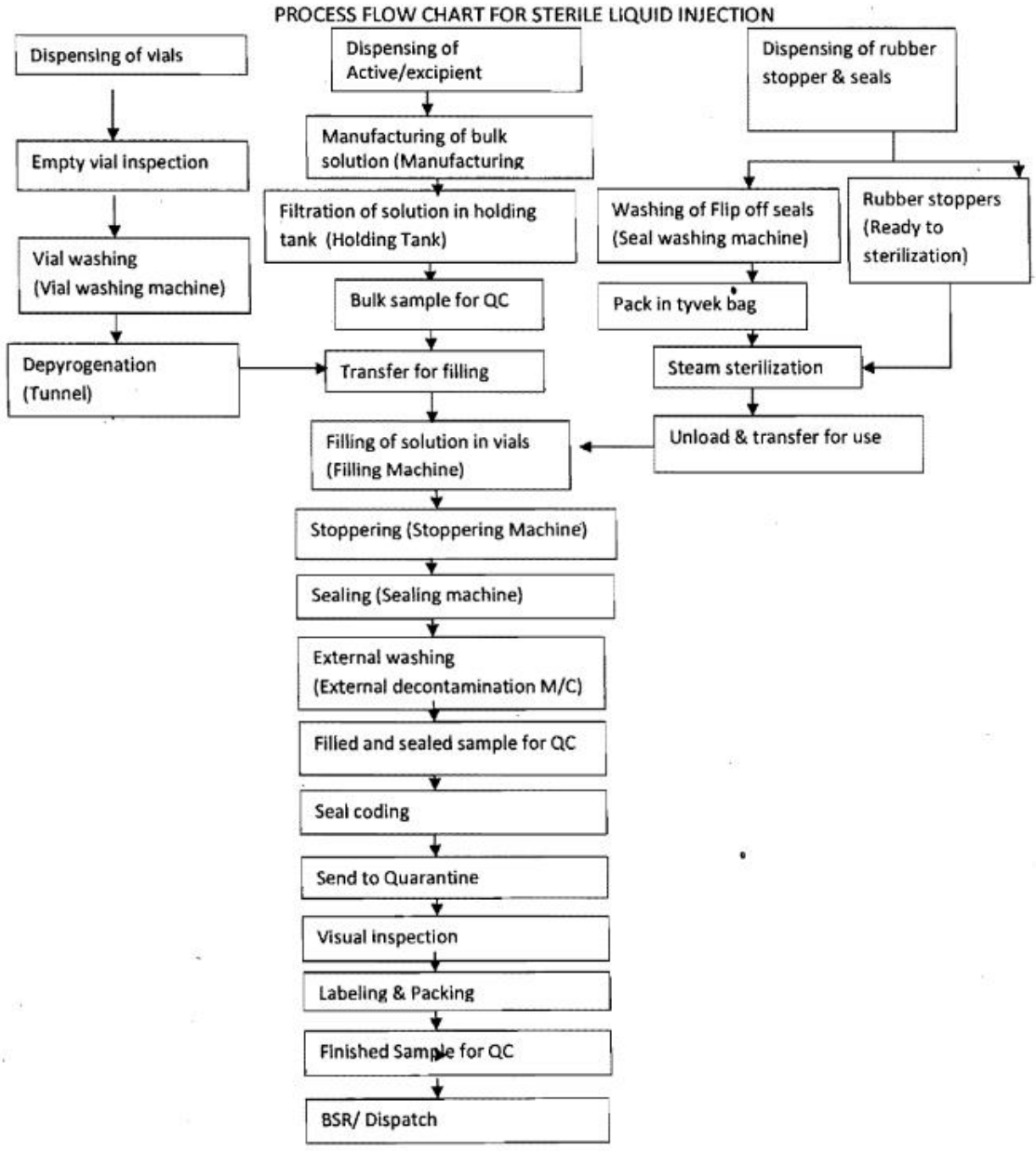
All regulations and SOPs concerning protection, manipulations, and clearance should be followed strictly and with high level of discipline and responsibility by the staff.

1. List of Equipment

S.NO.	NAME OF EQUIPMENT OF PRODUCTION	ID. CODE NO.
1.	HYDRA 1000-7B LINER WASHER	ONI/HLW/001
2.	BLUE GALAXY 550FL TUNNEL	ONI/BGF/001
3.	STERIFILL 100 FILLING MACHINE	ONI/SFM/001
4.	STERICAP100 STOPPERING MACHINE	ONI/SCS/001
5.	STERIPOUCH SEALING MACHINE	ONI/SSE/001
6.	LYOFAST AND INDUSTRIAL FREEZE DRYER	ONI/LYO/001
7.	AUTOCLAVE (900X900X1200) MM	ONI/ACL/001
8.	SAMPLING ISOLATOR	ONI/ISL/001
9.	CLASS 100 MOBILE TROLLEY	ONI/MTR/001
10.	FULLY AUTOMATED INTEGRITY TESTING DEVICE	ONI/FAI/001
11.	MANUFACTURING TANK 100LTR	ONI/MTK/001
12.	LABELLING MACHINE	ONI/LAM/001
13.	PERISTALTIC PUMP	ONI/PSP/001
14.	MAGNETIC STIRRER	ONI/MSR/001
15.	ANALYTICALBALANCE	ONI/ABL/001
16.	ANALYTICALBALANCE	ONI/ABL/002
17.	ANALYTICALBALANCE	ONI/ABL/003
18.	ANALYTICALBALANCE	ONI/ABL/004
19.	ANALYTICALBALANCE	ONI/ABL/005
20.	BIOSAFETY CABINET	ONI/BSC/001
21.	VISUAL INSPECTION BOOTH	ONI/VIB/001
22.	VISUAL INSPECTION BOOTH	ONI/VIB/002
23.	LAMINAR AIR FLOW	ONI/LAF/001

24.	LAMINAR AIR FLOW	ONI/LAF/002
25.	PH METER	ONI/PHM/001
26.	SHRINK WRAPPING MACHINE	ONI/SWM/001
27.	PLASTIC STRAPPING MACHINE	ONI/PSM/001
28.	DISPENSING ISOLATOR	ONI/DIS/001
29.	GARMENT WASHING MACHINE	ONI/GWM/001
30.	GARMENT DRYING MACHINE	ONI/GDM/001
31.	DYNAMIC PASS BOX- 1	ONI/DPB/001
32.	DYNAMIC PASS BOX -2	ONI/DPB/002
33.	DYNAMIC PASS BOX -3	ONI/DPB/003
34.	STATIC PASS BOX	ONI/SPB/001
35.	PACKING CONVEYER BELT	ONI/PCB/001
36.	CARTON CODING MACHINE	ONI/CCM/001
37.	FOGGER	ONI/FOG/001
38.	PNEUMATIC TRAY LOADING PLATFORM	ONI/PTP/001
39.	BOPP TAPPING MACHINE	ONI/BOP/001
40.	PRESSURE VESSEL 25 L	ONI/FFV/001
41.	PRESSURE VESSEL 25 L	ONI/FFV/002
42.	PRESSURE VESSEL 200 L	ONI/FFV/003
43.	PRESSURE VESSEL 200 L	ONI/FFV/004
44.	REFRIGERATOR	ONI/RFR/001
45.	REFRIGERATOR	ONI/RFR/002
46.	HIGH PRESSURE HOMOGENIZER	ONI/HPH/001

2. Flow diagram of Manufacturing process



3. Narrative Description of the Manufacturing Process

1 Manufacturing Process Description

1.1 Decartoning of vials.

1.2 Inspection of Vials.

1.3 Washing and De-pyrogenation of vials.

1.4 Washing, Siliconization, Sterilization and drying of rubber plugs.

1.5 Autoclaving of seals.

1.6 Washing and Sterilization of Machine Parts.

1.7 Weighing & verification of quantity of raw material & transfer to filling area

1.8 Preparation of Bulk Solution

1.9 Vial Filling and Stoppering

1.10 Vial Sealing

1.11 Visual Inspection.

1.12 In process Quality Control Checks

1.13 Labeling & Packaging.

P 3.4 Control of Critical Steps and Intermediate

Steps	Controls	Acceptance criteria
Dispensing of Raw material	Controlled Area	Temperature: 25±2°C Humidity: NMT 55%
Dispensing of Primary packing material	Controlled Area	Temperature: 25±2°C Humidity: NMT 55%
Washing of vials	Filtered air pressure, Reprocessed water pressure, Filtered WFI Pressure	Not Less Than 2.0 kg/cm^2 Not Less Than 2.0 kg/cm^2 Not Less Than 2.0 kg/cm^2
Depyrogenation of vial	Conveyor speed, Drying zone, Sterilizing zone, Cooling zone,	0-132mm/min Not Less Than 30°C Not Less Than 310°C Not Less Than 30°C
Filling	Fill volume	Not Less Than 50ml
Sealing	Leak test, Clarity test	Vials should pass the test Vials should be clear

P 3.5 Process Validation and/or Evaluation

First three commercial scale batches are subjected to Process Validation studies as per the protocol.

During the manufacturing process the different production steps are supervised by suitable in-process controls, which guarantee the consistency in properties within the finished product.

S. No.	Batch Number	Mfd. Date	Expiry Date
1.	TOI19034	03/2019	02/2021
2.	TOI19035	03/2019	02/2021
3.	TOI19036	03/2019	02/2021

P 4 CONTROL OF EXCIPIENTS

P 4.1 Specifications

Sr. No.	Ingredient	Specifications or Reference
1.	Polyoxyl 35 castor oil	USP
2.	Citric acid	USP
3.	Dehydrated alcohol	USP

Specifications of the above excipients are provided.

P 4.2 Analytical Procedures

Sr. No.	Ingredient	Specifications or Reference
1.	Polyoxyl 35 castor oil	USP
2.	Citric acid	USP
3.	Dehydrated alcohol	USP

P 4.3 Validation of analytical procedures

Not applicable

P 4.4 Justifications of specifications

All excipients are as per USP

P 4.5 Excipients of Human and Animal Origin

Not applicable

P 4.6 Novel Excipients

Not applicable

P 5 CONTROL OF FINISHED PRODUCTS

P 5.1 Specifications

Sr. No.	Test	Specifications
1	Description	A clear colourless to slight yellow viscous solution packed in 50 ml USP type I amber color glass vial.
2	Identification A. B.	The retention time of the major peak in the chromatogram of the test solution corresponds to that in the chromatogram of the standard solution, as obtained in test for limit of degradation products. The retention time of the major peak in the chromatogram of the test solution corresponds to that in the chromatogram of the standard solution, as obtained in test for limit of Assay.
3	Extractable volume	The volume should not less than the nominal volume.
4	Particulate matter Visual particulate Sub-visible particles	 Injection should be clear and practically free from particles that can be observed on visual inspection by the unaided eye. The average number of particles present in the units tested does not exceed 6000 per container equal to or greater than 10µm and does not exceeds 600 per container equal to or greater than 25µm.
5	pH	3.0 to 7.0
6	Limit of degradation products: Baccatin III at RRT 0.19 Ethyl ester side chain at RRT 0.21 10-Deacetylpaclitaxel 10-Deacetyl-7-epipaclitaxel (Paclitaxel related compound B) 7-Epipaclitaxel Any other Paclitaxel degradation product Total Paclitaxel degradation product	 NMT 0.8% NMT 0.4% NMT 0.8% NMT 0.5% NMT 0.6% NMT 0.1% NMT 2.0%
7	Assay	

	Each ml Contains: Paclitaxel USP----6mg	Not less than 5.4 mg and not more than 6.6 mg. (NLT 90% and NMT 110%).
8	Bacterial Endotoxin	Not more than 0.67 USP Endotoxin Unit per mg of Paclitaxel.
9	Sterility	Shall Comply for sterility test

P 5.2 Analytical Procedures

Analytical Procedures of the finished Paclitaxel injection USP 300mg/50ml is provided in Module 3.

P 5.3 Validation of Analytical Procedures

Validation of Analytical procedure is used for assay determination of Paclitaxel injection USP with established specification, provide accurate, reliable and reproducible results

The validation includes establishment & performance characteristics of an analytical method for determination of assay content in Paclitaxel injection USP by HPLC.

The method has been validated for following parameters:

- System Suitability
- Linearity
- Range
- Precision

Validation of Analytical Procedures of the finished product (Paclitaxel injection USP) is provided in Module 3.

P 5.4 Batch Analyses

Sr. No.	Batch No.	Batch Size	Manufacturing Date	Expiry Date
1	OIE23038	1000 Vials	07/2023	06/2025
2	OIE23039	1000 Vials	07/2023	06/2025
3	OIE23040	1000 Vials	07/2023	06/2025

Test	Specifications	Observations		
		Batch no. OIE23038	**Batch no. OIE23039**	**Batch no. OIE23040**
Description	A clear colourless to slight yellow viscous solution packed in 50 ml USP type I amber color glass vial.	A clear colourless viscous solution packed in 50 ml USP type I amber color glass vial.	A clear colourless viscous solution packed in 50 ml USP type I amber color glass vial.	A clear colourless viscous solution packed in 50 ml USP type I amber color glass vial.
Identification A.	The retention time of the major peak in the chromatogram of the test solution corresponds to that in the chromatogram of the standard solution, as obtained in test for limit of degradation products.	Identified	Identified	Identified
B.	The retention time of the major peak in the chromatogram of the test solution corresponds to that in the chromatogram of the standard solution, as obtained in test for limit of Assay.	Identified	Identified	Identified
Extractable volume	The volume should not less than the nominal volume.	50.1 ml	50.1 ml	50.2 ml
Particulate matter A. Visual particulate	Injection should be clear and practically free from particles that can be observed on visual inspection by the unaided eye.	Complies	Complies	Complies
B. Sub-visible particles	The average number of particles present in the units tested does not exceed 6000 per container equal to or greater than 10µm and does not exceeds 600 per container equal to or greater than 25µm.	Complies	Complies	Complies
pH	3.0 to 7.0	4.846	5.078	5.114
Limit of degradation products: Baccatin III at RRT 0.19 Ethyl ester side chain at RRT 0.21 10-Deacetylpaclitaxel 10-Deacetyl-7-epipaclitaxel (Paclitaxel related compound B) 7-Epipaclitaxel Any other Paclitaxel degradation product Total Paclitaxel degradation product	 NMT 0.8% NMT 0.4% NMT 0.8% NMT 0.5% NMT 0.6% NMT 0.1% NMT 2.0%	 ND ND ND ND ND 0.012% 0.16%	 ND ND ND ND ND 0.007% 0.14%	 ND ND ND ND ND 0.009% 0.14%

Assay Each ml Contains: Paclitaxel USP---- 6mg	Not less than 5.4 mg and not more than 6.6 mg. (NLT 90% and NMT 110%).	5.994mg (99.91%)	5.989mg (99.83%)	5.987mg (99.79%)
Bacterial Endotoxin	Not more than 0.67 USP Endotoxin Unit per mg of Paclitaxel.	Less than 0.67 EU/mg	Less than 0.67 EU/mg	Less than 0.67 EU/mg
Sterility	Shall Comply for sterility test	Sterile	Sterile	Sterile

P 5.5 Characterization of Impurities

Impurities	Limit	Origin
Baccatin III at RRT 0.19 Ethyl ester side chain at RRT 0.21 10-Deacetylpaclitaxel 10-Deacetyl-7-epipaclitaxel (Paclitaxel related compound B) 7-Epipaclitaxel Any other Paclitaxel degradation product Total Paclitaxel degradation product	NMT 0.8% NMT 0.4% NMT 0.8% NMT 0.5% NMT 0.6% NMT 0.1% NMT 2.0%	Based on USP monograph

P 5.6 Justification of Specifications

There is official monograph available for Paclitaxel injection USP 300mg/50ml is developed as per USP standards. Specifications have been set on the basis of USP data.

P 6 Reference Standards or Materials

The following working standard is used in the analysis of Paclitaxel injection USP 300mg/50ml.

S. No.	Reference Standard	Reference Std. Batch No.	Assay
1.	Paclitaxel USP	R04650	0.994 mg

P 7 Container Closure System

The Container/Closure System used in Paclitaxel injection USP 300mg/50ml is given below:

Sr. No.	Packing	Container/closure system(s)
1	Primary Packing Material	Glass Vial, Rubber Plug, Flip off Aluminum Seal

2	Secondary packaging materials	Carton, Leaflet, Label

P 8 Stability

P 8.1 Stability summary and conclusion

Objective

The purpose of the study is to evaluate and document the influence of various environments Factors (Temperature & Humidity) on the quality of the Paclitaxel injection USP 300mg/50ml to support proposed shelf life of 24 Months+12months. The study will be carried out on three batches of injection at long term Condition as well as accelerated condition. Further one batch will be repeated in long term Storage condition in marketable pack on annual basis.

Selection of Batches

Initially three batches are kept for stability analysis of new drug. The batches should be manufactured to a minimum of pilot plant scale and by the same synthetic route as for manufacturing process. Then one batch is kept every year for long term stability analysis only.

Storage condition and time:

The stability analysis is performed at the following storage conditions.

Sr. No.	Storage Conditions	Temperature	Storage Time
1	Accelerated	40 ± 2° C/75 ± 5% RH	Initial, 3M, 6M,
2	Long-term	30 ± 2° C/75 ± 5% RH	Initial, 3M, 6M, 9M, 12M, 18M, 24M, 36M

Batches tested in finish product stability

Batch No.	Packing	Manufacturing Date	Expiry Date	Manufacture	Batch Size
TOI19034	Clear colourless viscous solution is filled in 50 ml USP type I amber glass	03/2019	02/2021	Cosmas Research Lab. Ltd.	1000 Vials
TOI19035		03/2019	02/2021		

TOI19036	vial with rubber stopper and flip-off aluminium seal. Such 1 labeled vial is packed in printed carton along with pack insert.	03/2019	02/2021		

Synopsis and conclusion of the studies of stability:

Stability Study of Paclitaxel injection USP 300mg/50ml was performed to assess the physical and chemical stability in the proposed primary pack, when exposed to varying environmental conditions in order to assign the shelf life to the product.

Results

The test results of the study are presented in the tables attached.

Discussion / Conclusions:

Storage under long term testing conditions causes insignificant change of assay results of Paclitaxel. Significant changes in physical and chemical stabilities were not observed. Since the long-term data and accelerated data show no change over time and little variability, a statistical analysis is considered unnecessary.

P 8.2 Post - approval stability protocol and stability commitment

The stability studies are continued in order to firmly establish the re-test period of the product. Besides completion of stability study for current batches, minimum one batch every year will be kept for long term stability studies. If any major changes are made in the manufacturing process and/or the equipment, the stability testing will be conducted for accelerated and long term conditions on minimum one production batch after the changes.

P 8.3 Stability Data

Stability Data is provided in module 3.

3.2.A Appendices

3.2.A.1 Facilities and equipments

Site master file is enclosed in Module 3 Section 3.2.A.1.

3.2.A.2 Adventitious agents' safety evaluation

Not applicable

3.2.A.3 Excipient

No novel excipients are present in this formulation.

3.2.R Regional information

3.2.R.1 Production documentation

3.2.R.1.1 Executed production documents

Executed BMR will be as per Master BMR.

3.2.R.1.2 Master production documents

The blank master production documents for each strength, proposed commercial batch size and manufacturing facility is provided in Module 3.

3.2.R.2 Analytical procedures and validation information

ANALYTICAL PROCEDURES AND VALIDATION INFORMATION SUMMARIES			
ATTACHMENT NUMBER: QC/FPT/5041/00			
HPLC Method Summary		**Volume/Page:**	3
Method name:	Assay		
Method code:	7	**Version and/or Date:**	Standard analytical procedure
Column(s) / temperature (if other than ambient):		L-43 (250 x 4.0) mm, 5µm.	
Mobile phase (specify gradient program, if applicable):		Transfer 200 µl of glacial acetic acid to a 1 liter volumetric flask containing about 500 ml of methanol mix and dilute with methanol to volume.	
Detector (and wavelength, if applicable):		UV VIS	
Flow rate:		1.5 ml per minute	
Injection volume:		10 µl	
Sample solution preparation and concentration (expressed as mg/ml, let this be termed "A"):		0.6 mg/ml	
Reference solution preparation and concentration (expressed as mg/ml and as % of "A"):		0.6 mg/ml	
System suitability solution concentration (expressed as mg/ml and as % of "A"):		NA	
System suitability tests (tests and acceptance criteria):		NA	
Method of quantification (e.g. against API or impurity reference standard(s)):		Against API	
Other information (specify):		Not available	

2.4 Non clinical overview

Not applicable

2.5 Clinical overview

Not applicable

2.6 Non clinical summary

Not applicable

2.7 Clinical summary

Not applicable