PROCESS VALIDATION PROTOCOL

PRODUCT NAME

FLUOURACIL INJECTION BP

50MG/ML, 20ML

STANDARD BATCH SIZE

50.0 Liters (2500 Vials)

PROTOCOL NO.

FU/PVP/001-00

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1. PROTOCOL APPROVAL

Signing of this approval page of process validation Protocol No. FU/PVP/001-00 indicates agreement with the Process Validation Approach described in this document. Any modification to the process validation will be prepared and approved as an addendum.

Prepared By

Name	Designation	Signature	Date
Vinayak Kaushal	Officer QA		02/08/21

Checked By

Name	Designation	Signature	Date
Harpinder Singh	Executive		02/08/21
Prosenjit Chatterjee	Production Head		02/08/21
B.B. Pandey	Engg Manager	B.B. Pandey	02/08/21
Naresh Kumar	Head QC		02/08/21

Approved By

Name	Designation	Signature	Date
Akhil Sharma	Dy. Manager QA		03/08/21

Authorized By

Name	Designation	Signature	Date
N.P. Mishra	Head QA		03/08/21

2. OBJECTIVE:

To conduct the process validation of the manufacturing process for the **Fluorouracil Injection BP 50mg/ml, 20ml** manufactured at cytotoxic Injection block. The validation study shall be conducted for the generation of sufficient data to establish documentary evidence and to provide assurance that the product can be manufactured on a commercial scale, meeting all its quality attributes in a consistent manner.

3. SCOPE:

This protocol shall be applicable for first three consecutive batches manufactured with specific batch size and equipment and operating parameters for the **Fluorouracil Injection BP 50mg/ml, 20ml** at Kwality Pharmaceuticals Limited Raja Ka Bagh.

4. VALIDATION APPROACH:

The validation approach shall be prospective and following things shall be reviewed:

4.1 Review the qualification documents of equipment and related utility systems which shall be employed for the manufacturing of batch.

4.2 Review the Analytical method validation.

4.3 Review the calibration record of instruments used in validation.

4.4 Review the master formula records.

4.5 Review the specification and analytical procedures of raw materials and packing materials.

4.6 Review the specification and analytical procedures for in-process & finished products.

5. REASON FOR VALIDATION:

Process Validation shall be carry out due to modification in equipments.

6. REVALIDATION:

The manufacturing process is subjected to revalidation when following changes occur.

1. When change in quantity and change in Excipients
2. Any Change in batch size
3. Change in master formula.
4. Change in manufacturing site
5. Any modification in any critical equipment
6. Any change in the specification and change in the source of active Pharmaceuticals Ingredient.
7. Any change in primary packing material
8. Any major change in the manufacturing process which may affect the quality of the product.

7. RESPONSIBILITY:

Following validation team is responsible for carried out process validation.

7.1 Quality Assurance shall be responsible for:

- Preparation, approval and training of validation protocol, review of the data compiled, review of deviations (if any), monitoring the process as per the process parameters and for withdrawal of validation samples.
- Review of facility, equipment qualification and utility validation reports.
- cGMP compliance during the manufacturing process, review and evaluation of the data/results generated during the validation process.
- Preparation of process validation summary report, review and its approval.

7.2 Production shall be responsible for:

- To execute the batches as per the batch production record and process validation protocol.
- Compilation of data related to manufacturing area and furnishing the same for review.
- Review of protocol and summary report.

7.3 Quality Control shall be responsible for:

- Raw material and packing material analysis.
- In process and finished product samples analysis as per the sampling plan.
- Collection and review of in process and finished product analysis data.
- Submission of data /results to QA for review and evaluation.
- Review of Protocol and summary report.

7.4 Engineering shall be responsible for:

- For smooth working of the utilities.
- Review of Process Validation Protocol and summary report.

7.5 Microbiology shall be responsible for:

- Microbial analysis of product samples.

7.6 Head QA

- Head QA shall be responsible for the authorization process Validation Protocol and summary report.

8. Product & Batch Detail:

Process Validation of **Fluorouracil Injection BP 50mg/ml, 20ml** shall be carried out on any three consecutive batches.

The details are as under:

Product/ Generic Name	**:**	**Fluorouracil Injection BP**
Strength	**:**	50mg/ml, 20ml
Product Code	**:**	FU/001
Batch Size	**:**	50.0 Liters
Dosage Form	**:**	Sterile Liquid Injection
Overage	**:**	Nil
Composition	**:**	Each ml contains: Fluorouracil BP 50 mg Water for Injection q.s.
Packing Detail	**:**	A clear colourless solution filled in 10 ml clear moulded vial USP type-1 stoppered with 20mm non slotted Bromo butyl rubber plug and 20 mm aluminium flip off seal having blue color.
Storage Condition	**:**	Store at temperature below 30°C. Protect from light.

Batch Detail for validation

3 consecutive batches are selected

Sr. No.	Batch No.	Batch Size	Batch Manufacturing Date	Mfg. Date	Exp. Date
1.					
2.					
3.					

9. Equipment and Machinery List

9.1 Production Equipment

Sr. No	Equipment Name	Make	Equipment Id. No.
1.	Sampling & Dispensing Isolator	Klenzide	KPL/WH/013
2.	Reverse Laminar Air Flow	New Brehz Engineering Works	KPL/WH/005
3.	Weighing Balance	A & D company Limited	KPL/WH/006
4.	Vial washing machine	Kailas machine tools	KPL/CI/010
5.	Bung Washing Machine	Parth Engineering	KPL/CI/011
6.	Homogenizer	IKA	KPL/CI/017
7.	Pressure Vessel –I	————	KPL/CI/018
8.	Pressure Vessel –II	————	KPL/CI/019
9.	Pressure Vessel –III(Jacketed)	————	KPL/CI/020
10.	Pressure Vessel –IV	————	KPL/CI/021
11.	SS 316 Membrane Holder-I	————	KPL/CI/022
12.	SS 316 Membrane Holder-II	————	KPL/CI/023
13.	SS 316 Membrane Holder-III	————	KPL/CI/024
14.	Automatic Vial Filling Machine	Keshav Pharmapack	KPL/CI/025
15.	Sealing machine	Keshav Pharmapack	KPL/CI/026
16.	Rotary Evaporator	IKA	KPL/CI/027
17.	Cold Room	Blue Star	KPL/CI/028
18.	Bubble point tester	Pall life science	KPL/CI/029
19.	Compounding Isolator	Klenzaids	KPL/CI/030
20.	Lyophilizer-I	Lyophilization System India	KPL/CI/031
21.	Lyophilizer-II	Lyophilization System India	KPL/CI/032
22.	Manufacturing Tank –I	Komal	KPL/CI/033
23.	Manufacturing Tank –II	Komal	KPL/CI/034
24.	Fogger	————	KPL/CI/035
25.	Three bucket system	————	KPL/CI/036
26.	Vacuum pump	————	KPL/CI/039
27.	Closer Processing System Cum HPHV	Machin Fabrik	KPL/CI/040

Sr. No	Equipment Name	Make	Equipment Id. No.
28.	Dynamic Pass Box –I	P.S. Air Technology	KPL/CI/041
29.	Dynamic Pass Box –II	P.S. Air Technology	KPL/CI/042
30.	Dynamic Pass Box –III	P.S. Air Technology	KPL/CI/043
31.	Dynamic Pass Box –IV	P.S. Air Technology	KPL/CI/044
32.	Dynamic Pass Box –V	P.S. Air Technology	KPL/CI/045
33.	Dynamic Pass Box –VI	P.S. Air Technology	KPL/CI/046
34.	Dynamic Pass Box –VII	P.S. Air Technology	KPL/CI/047
35.	Dynamic Pass Box –VIII	P.S. Air Technology	KPL/CI/048
36.	Mobile Trolley- I	P.S. Air Technology	KPL/CI/049
37.	Mobile Trolley-II	P.S. Air Technology	KPL/CI/050
38.	Sterile garments cubicle -I	————	KPL/CI/051
39.	Sterile garments cubicle -II	————	KPL/CI/052
40.	Laminar Air Flow	P.S. Air Technology	KPL/CI/053
41.	Particle Counter	Shreedhar instruments	KPL/CI/054
42.	Laminar Air Flow	P.S. Air Technology	KPL/CI/055
43.	Laminar Air Flow	P.S. Air Technology	KPL/CI/056
44.	Laminar Air Flow	P.S. Air Technology	KPL/CI/057
45.	Laminar Air Flow	P.S. Air Technology	KPL/CI/058
46.	Laminar Air Flow	P.S. Air Technology	KPL/CI/059
47.	Laminar Air Flow	P.S. Air Technology	KPL/CI/060
48.	Laminar Air Flow	P.S. Air Technology	KPL/CI/061
49.	Laminar Air Flow	P.S. Air Technology	KPL/CI/062
50.	SS Membrane holder	————	KPL/CI/066
51.	Housing filter	————	KPL/CI/067
52.	Table Mount LAF	————	KPL/CI/074
53.	Laminar Air Flow	P.S. Air Technology	KPL/CI/075
54.	Dry Heat Sterilizer	Machine Fabrik	KPL/CI/076

9.2 Engineering Equipment

Sr. No	Equipment Name	Make	Equipment Id. No.
55.	Purified Water system	Komal	KPL/ENG/014
56.	Water spifor Injection System	Komal	KPL/ENG/015
57.	Pure steam System	Komal	KPL/ENG/016
58.	Compressed Air System	Ingersoll Rand	KPL/ENG/001
59.	Nitrogen System	Allied Air and gas Engineers	KPL/ENG/007
60.	Air Handling Unit	ZECO	AHU/HAC02/CI/001
61.	Air Handling Unit	ZECO	AHU/HAC02/CI/004
62.	Air Handling Unit	ZECO	AHU/HAC02/CI/005
63.	Air Handling Unit	ZECO	AHU/HAC02/CI/006
64.	Air Handling Unit	ZECO	AHU/HAC02/CI/007
65.	Air Handling Unit	ZECO	AHU/HAC02/CI/008
66.	Air Handling Unit	ZECO	AHU/HAC02/CI/009
67.	Air Handling Unit	ZECO	AHU/HAC02/CI/010
68.	Air Handling Unit	ZECO	AHU/HAC02/CI/011

9.3 Quality Control Instrument

Sr. No	Equipment Name	Make	Equipment Id. No.
1.	High Performance Liquid Chromatography	Shimadzu LC	KPL/QC/117
2.	High Performance Liquid Chromatography	Shimadzu	KPL/QC/118
3.	Weighing Balance	Shimadzu	KPL/QC/054

10. Raw Material Sheet:

Batch Size: 50.0 Liters (2500 Vials)

Name of Ingredients	Specifications	Std. Qty per ml	O.A (%)	Qty required for Batch
Fluorouracil	BP	50.00 mg	Nil	2.500 kg
Disodium edetate	BP	1.00 mg	Nil	0.050 kg
Tromethamine	BP	84.00 mg	Nil	4.200 kg
Sodium Hydroxide	BP	6.00 mg	Nil	0.300 kg
Sodium Hydroxide	BP	q.s. to pH adjustment	Nil	q.s. to pH adjustment
Water for Injection	BP	q.s. to 1 ml	Nil	50.0 ltr

*** Actual quantity of Fluorouracil depends on assay basis.**

Average Fill Volume: NLT 20 ml

11. Approved Raw and Packing Material:

The raw or packing material uses in manufacturing process are from approved vendor.

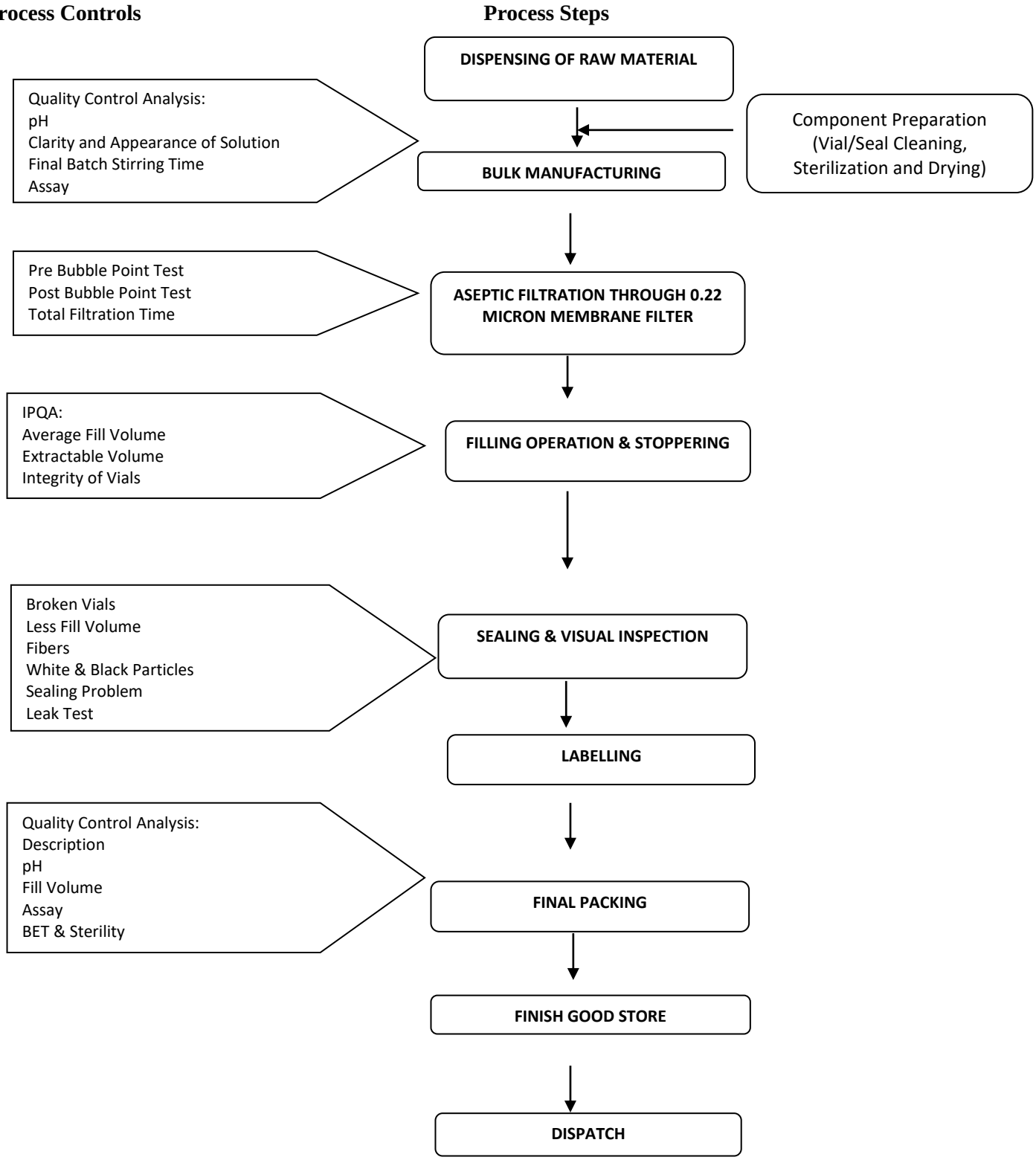
Raw Material:

Raw Material	Spec.	Item Code	Vendor
Fluorouracil	BP	AC/130R	Avandose Pharmatech Ltd.
Disodium edetate	BP	E/0216	Prachin Chemical
Tromethamine	BP	E/0228	MP Biomedicals Pvt. Ltd.
Sodium Hydroxide	BP	E/0157	Avarice Quality Delivered
Water for Injection	BP	E/0084	Self

Packing Material:

Packing material	Spec.	Item Code	Vendor
20 ml clear moulded Glass vial USP type 1	IHS	P/V/003	Piramal Glass Pvt. Ltd.
20 mm Gray Bromo Butyl rubber Stopper	IHS	P/S/006	Bharat Rubber Works Pvt. Ltd
20 mm flip off seal blue colour	IHS	P/S/008	Shakai Packaging Private Limited

12. Process Flow Diagram



13. Manufacturing process

Check the Equipment for Cleanliness prior to use before manufacturing process and check the status label displayed.

Take line clearance from IPQA for cleanliness

Sr. No.	Procedure For Bulk Preparation
1	Take freshly collected Water for Injection in dry and cleaned sterile S.S. manufacturing tank and cool at temperature between 30ºC - 40ºC with Continue nitrogen purging throughout the compounding process.
2	Now transfer Disodium edetate in manufacturing tank with continues stirring until a clear solution is obtained and check the clarity of the solution.
3	Now add Tromethamine in manufacturing tank with continues stirring and clear the solution.
4	Stir the solution for 20 minutes and check the complete dissolution and clarity of the solution.
5	Add fluorouracil in manufacturing tank and continue stirring to disperse it completely.
6	Now add sodium hydroxide slowly in manufacturing tank under continues stirring and stir the solution to obtain clear solution.
7	Check the pH of the solution in between 8.5-9.1. If required adjust the pH of solution with sodium hydroxide.
8	Make up the final batch volume_____ liters with water for injection.
9	Send the Sample to QC for chemical analysis (Attach the bulk report in the BMR). If results found within limit than proceed further process.

Speed S.S. Mechanical Stirrer (RPM)	Sample Volume (ml)	Appearance and Clarity of Solution	pH	Final Batch Stirring Time
1500	20 ml each at different stirring time	A Clear colourless solution	8.5 to 9.1	10 minutes
				15 minutes
				20 minutes

Test	Nitrogen Pressure
Pre Bubble Point Test	1.2 kg/cm^2 to 1.5 kg /cm^2
Post Bubble Point Test	1.5 kg/cm^2 to 1.8 kg /cm^2

14. Filling & sealing:

1. After Bubble point test, take line clearance from IPQA personal for Filling and partial plugging and for the machines and equipments to be used during the filling and partial plugging. Total Filtration Time shall be recorded.
2. Set the Filling and Sealing Machine at slow, medium & high speed and aseptically fill not less than 10 ml of Solution in 10 ml clear moulded vial. Inform IPQA personal for sampling of Filled Vials.

Sample Quantity	Average Fill Volume	Extractable Volume	Integrity of Vials
10 Vials at the beginning, middle and end of operation	NLT 20 ml	NLT 20 ml	Should be properly Plugged

3. IPQA personal shall draw 10 Vials for Sample at the beginning, middle and end of the filling operation and carry out in process check for individual fill volume, minimum and maximum and average fill volume.

15. Visual Inspection

1. Remove the Plugged Vials aseptically from the Lyophilizer and Seal the Vials with Aluminium Flip off Seal having Red colour.
2. Filled and Sealed Vials are inspected against white and black board to check the absence of any extrinsic particles such as glass pieces, fibbers, white and black particles and less volume and other physical defects such as broken vials and improper sealing at the beginning, middle and end of the filling and sealing operation at different speed of sealing machine.
3. Inform the IPQA personal for Sampling of Filled and Sealed vials for Optical Inspection. Following Parameters are to be checked during the Optical Inspection.

Sample Quantity	Physical Defects / Rejections	Results
10 Vials at the beginning, middle and end of operation	Broken Vials Less Volume Fibers White Particles Black Particles	Should be Nil

16. Sampling Plan:

S. No.	Stage	Sampling time/ Qty.	Test/ Process Parameter	Acceptance Record
1.	**Vial Washing**	Before Washing (20 Vials)	Bio Burden	For informative purpose
		After Washing (20 Vials)	Bio Burden	For informative purpose
		After Depyrogenation Initial, middle & end (21 Vials)	Sterility Bacterial Endotoxin Sterilization Temperature and time	To be comply NMT 0.33 EU At 250 ˚C hold for 120 minutes.

		Purified water	pH, conductivity, description & QC specification.	As per QC limits
		Water for injection	pH, conductivity, description & QC specification.	As per QC limits
2.	**WFI Collection**	After collection (100 ml)	BET, pH, Conductivity, Description, Bioburden	To be comply as per water for injection specification
3.	**Manufacturing**	During mixing after 10 , 15 and 20 minutes (20 ml each stage)	For Description, Assay and pH	Comply as per QC bulk specification
		Bioburden (20 ml)	1000 cfu / ml (As per QC specification)	As per QC limits
4.	**Filtration**	After filtration (20 ml for each)	From filling vessel Sterility	As per QC limits
			For Description, Assay and pH	
5.	**Filling & sealing**	Initial Middle & end (02 vials at each stage)	Fill Volume (Every 30 minutes) Assay pH Leak Test	NLT 20 ml Comply as per QC bulk specification Complies as per Grade A Should be sterile.
		Before filling & sealing	Viable & non viable count	
		Nitrogen	Sterility	Complies as per ISO 8573 Class 2.
		Initial, middle & end (22 bungs at each stage)	Sterility and BET	As per QC limits
		Initial Middle & end (20 vials at each stage)	Sterility	As per QC limits
		Initial Middle & end (20 flip off seal at each stage)	Sterility	As per QC limits
6.	**Visual Inspection**	Initial Middle & end	Broken Vials Less Volume Fibers White Particles Sealing problem Black Particles	Should be Absent or Nil

7.	**Finish product Analysis**	Composite sample (45 vials)	Complete testing as per finish product specification	Comply as per QC finish specification

17. HOLD TIME STUDY SAMPLING PLAN

Note: The sampling duration is to be taken for initial, middle & end of the manufacturing procedure to bracketing the complete time period of manufacturing. It is to be established that the complete manufacturing procedure has been performed in a consistent manner.

All critical process parameter is to be estabilished by challenging the parameters range with respect to the Batch Manufacturing Record.

Sr. No	Stage	Interval	Sample Quantity	Test	Acceptance Criteria
01	**Before Filtration (From Manufacturing tank)**	0 Hour, 6 Hour, 12 Hour	20 ml (each stage)	For Chemical Analysis (Description, Assay and pH)	As Per QC Specifications
			20 ml(each stage)	For Bio burden	As Per QC Specifications
02	**After Filtration (From Holding tank)**	0 Hour, 6 Hour, 12 Hour, 24 Hour, 48 Hour	20 ml (each stage)	For Chemical Analysis (Description, Assay and pH)	As Per QC Specifications
			20 ml(each stage)	For Sterility	As Per QC Specifications

18. JUSTIFICATION FOR SAMPLING PLAN

Sr. No.	Stage	Critical & Non Critical Process Variable	Impact on CPP	Sampling Point	Justification
1.	Bulk Manufacturing	Mixing Time, Stirring Speed	pH, Clarity of the Solution & Assay	From Compounding Vessel, during mixing after 10, 15 and 20 minutes (20ml each stage).	To evaluate the results of bulk sample at different mixing time.
2.	Aseptic Filtration	0.22 µ Filter Integrity, Pressure	Clarity of Solution, Sterility,	After filtration from filling vessel	To evaluate the results od

		applied & Filtration Time	pH & assay.	(20ml for each).	solution after filtration with 0.22 filter and applied pressure.
3.	Filling and Stoppering	Fill Volume stting, filling & Stoppering machine speed.	Average Fill Volume variation, Extractable Volume variation.	Initial, Middle & end (02 vials at each stage for fill volume, pH & Assay). And Initial, Middle & end (20 vials at each stage for Sterility)	For bracketing the complete time period of manufacturing and to estabilished the rational that complete manufacturing procedure has been performed in a consistent manner.
4.	Sealing & Visual Inspection	Sealing Speed, Sealing head height.	Integrity of Vials, Sealing Defects, Foreign Particles & Fill Volume.		

19. ACCEPTANCE CRITERIA

Stage	Test / Process parameter	Acceptance criteria
Bulk Manufacturing	Clarity and Appearance of Solution	To Verify the clarity and Appearance of bulk solution
	pH	8.5 to 9.1
	Assay	90.0 % to 110.0 %
Aseptic Filtration (Pre and Post Bubble Point Test and Total Filtration time)	N2 Pressure (Pre Bubble Point Test)	1.2 kg/cm^2 to 1.5 kg /cm^2 (Filter should not burst)
	N2 Pressure (Post Bubble Point Test)	1.5 kg/cm^2 to 1.8 kg /cm^2 (Filter should not chock and burst)
	Total Filtration Time	Within 15 minutes
Filling & Sealing	Average Fill Volume	NLT 20 ml
	Extractable Volume	NLT 20 ml
Visual Inspection	Broken Vials	Should be absent or Nil
	Less Volume	
	Fibers	
	White Particles	
	Black Particles	
	Sealing Problem	
Quality Control Attributes before labeling	Description	A clear colourless solution filled in 20 ml clear moulded vial USP type-1
	Identification	

Stage	Test / Process parameter	Acceptance criteria
	By IR	The infrared absorption spectrum obtained from the residue of sample should be concordant to the infrared absorption spectrum obtained from the working standard or reference standard.
	By UV	In the assay, the UV spectrum of sample solution should exhibit a maxima only at about 266nm.
	pH	8.5 to 9.1
	Container content for injection	NLT 20 ml
	Uniformity of dosage units	For L1 stage , AV =NMT 15 and for L2 stage , AV = NMT 25
	Sterility	No. growth should be observed
	Bacterial endotoxins test	NMT 0.33 EU/mg
	Particulate Matter	For 10 µm to less than 25µm-NMT 6000 particles For 25 µm to greater-NMT 600 particles
	Related Substances	
	Any Individual Impurity	Should complies
	5- Hydroxyuracil	Any spot corresponding to 5- hydroxyuracil in the chromatograph obtained with sample solution should be not more intense than the spot in the chromatogram obtained with 5- hydroxyuracil standard.

20. REFERENCE DOCUMENTS

S. No.	Document name	Document No.
1.	Batch Manufacturing Record	FU/BMR/001
2.	Product Standard Testing Procedure	KPL/STP/IN/031-00
3.	Stability Protocol	SSP/21/007
4.	Fluorouracil Standard testing procedure	KPL/STP/RM/025-00
5.	Disodium Edetate	BP Monograph
6.	Tromethamine	BP Monograph
7.	Sodium Hydroxide	KPL/STP/RM/029-00
8.	Water for injection	KPL/STP/WI/001

21. STABILITY :

If acceptance criteria at all the stages of 3 batches are satisfied, the process to be accepted as validated for manufacturing the Product at the site, Kwality Pharmaceuticals Limited. The Validation batches shall be introduced for complete stability studies as per stability protocol.

22. Deviation Report:

_____

_____

_____

23. Change Control:

Process Validation Protocol of Fluorouracil Injection BP 50mg/ml, 10ml is prepared with reference change control no. CC/21/08/QA/065.

24. Abbreviation:

KPL	:	Kwality Pharmaceuticals Ltd.
PVP	:	Process Validation Protocol
IPQA	:	In-process Quality Assurance
QA	:	Quality Assurance
mg	:	milligram
kg	:	Kilogram
ml	:	mille liter