FORM 1

(I) Basic Information

S. No.	Item	Details
1.	Name of the projects	Proposed Expansion By Lupin Ltd. At Block No. 21, Dabhasa.
2.	S.No.in the schedule	5 (f)
3.	Proposed capacity/ area/ length/ tonnage to be handled/ command area/ lease area/ number wells to be drilled	Additional – 884.6 MT/Annum
4.	New/ Expansion/ Modernization	Expansion
5.	Existing Capacity/ Area etc.	Existing capacity: 595.40 MT/Annum Existing plot area: 117293 m2
6.	Category of Project i.e. 'A' or 'B'	A
7.	Does it attract the general Condition? If yes, please specify.	Yes
8.	Does it attract the specific condition? If yes, Please Specify.	Yes
9.	Location	
	Plot/Survey/Khasra No.	Block No. 21
	Village	Dabhasa
	Tehsil / Taluka	Padra
	District	Vadodara
	State	Gujarat
10.	Nearest railway station/airport along with Distance in kms	Vadodara railway station: 15.7km Vadodara airport: 19.5 km
11.	Nearest Town, city, District Headquarters Along with distance in kms.	Vadodara: 15.7 km
12.	Village Panchayats, Zilla Parishad Municipal Corporation, Local body (complete postal addresses with telephone no's to be given)	Dabhasa Gram Panchayat Tal: Padra, Dist: Vadodara, Gujarat Tel: 02662-244471
13.	Name of the applicant	Snehal M. Sheth
14.	Registered address	159, CST Road, Kalina, Santacruz (E) Mumbai 400 098, Maharashtra, India
15.	Address for correspondence	Block No. 21, Vill: Dabhasa, Tal: Padra, Dist: Vadodara, State: Gujarat
	Name	Snehal M. Sheth
	Designation(Owner/Partner/CEO)	Site Head & General Manager – Manufacturing
	Address	Block No. 21, Vill: Dabhasa, Tal: Padra, Dist:

		Vadodara, State: Gujarat
	Pin Code	391 440
	E-mail	snehalsheth@lupinpharma.com
	Telephone No.	02662 – 306751
	Fax No.	02662 – 306305
16.	Details of Alternative Sites examined if any. Location of these sites should be shown on a topo sheet.	Not Applicable (NA) as proposed project is an expansion within the existing plot.
17.	Interlinked Project	No
18.	Whether separate application of interlinked project has been submitted?	NA
19.	If yes, date of submission	-
20.	If no, reason	-
21.	Whether the proposal involves approval/clearance under: if yes, details of the same and their status will be given (a) The Forest (Conservation) Act, 1980? (b) The Wildlife (Protection) Act, 1972? (c) The C.R.Z. Notification, 1991?	NA
22.	Whether there is any Government Order/Policy relevant/relating to the site?	No
23.	Forests land involved (hectares)	No
24.	Whether there is any litigation pending against the project and/or land in which the project is proposed to be set up? (a) Name of the Court (b) Case No. (c) Order/Directions of the Court, if any and its relevance with the proposed project.	No

(II) Activity

1. Construction, operation or decommissioning of the Project involving actions, which will cause physical changes in the locality (topography, land use, changes in water bodies, etc.)

S. No.	Information/Checklist confirmation	Yes/ No	Details thereof (with approximate quantities / rates, wherever possible) with source of information data
1.1	Permanent or temporary change in land use, land cover or topography including increase in intensity of land use (with respect to local land use plan)	No	Proposed project is an expansion and will be located within the boundaries of the existing plot.
1.2	Clearance of existing land, vegetation and	No	

	buildings?		
1.3	Creation of new land uses?	No	
1.4	Pre-construction investigations e.g. bore houses, soil testing?	No	As proposed is an expansion soil testing has already been done.
1.5	Construction works?	Yes	The construction area includes new production blocks and utility/ service blocks.
1.6	Demolition works?	No	
1.7	Temporary sites used for construction works or housing of construction workers?	No	Construction workers will not stay at site.
1.8	Above ground buildings, structures or earthworks including linear structures, cut and fill or excavations	Yes	All the process plants will have structures.
1.9	Underground works including mining or tunneling?	No	
1.10	Reclamation works?	No	
1.11	Dredging?	No	
1.12	Offshore structures?	No	
1.13	Production and manufacturing processes?	Yes	Manufacturing of Bulk drugs & intermediates. Kindly refer **Annexure-1** for list of products. **Annexure-2** for manufacturing processes.
1.14	Facilities for storage of goods or materials?	Yes	Warehouses & tank farm area shall be created.
1.15	Facilities for treatment or disposal of solid waste or liquid effluents?	Yes	• Yes, existing ETP shall be upgraded to handle effluent. • Treated effluent shall be sent to CETP as per approved contract. Remaining shall be recovered.
1.16	Facilities for long term housing of operational workers?	No	
1.17	New road, rail or sea traffic during construction or operation?	No	Existing infrastructure will be used.
1.18	New road, rail, air waterborne or other transport infrastructure including new or altered routes and stations, ports, airports etc?	No	
1.19	Closure or diversion of existing transport routes or infrastructure leading to changes in traffic movements?	No	
1.20	New or diverted transmission lines or pipelines?	No	

1.21	Impoundment, damming, culverting, realignment or other changes to the hydrology of watercourses or aquifers?	No	
1.22	Stream crossings?	No	
1.23	Abstraction or transfers of water form ground or surface waters?	Yes	Additional requirement of water shall be met by upgrading CGWB license quantities and balance by effluent recycling after treatment.
1.24	Changes in water bodies or the land surface affecting drainage or run-off?	No	
1.25	Transport of personnel or materials for construction, operation or decommissioning?	No	Insignificant impact. Site is currently operational. Employees use transport of company. Material transport during projects shall be staggered as per requirement. Truck carrying cement & sand will be cover with tarpaulins. Construction area will be barricaded by tin sheets. Operating personnel shall use company transport.
1.26	Long-term dismantling or decommissioning or restoration works?	No	
1.27	Ongoing activity during decommissioning which could have an impact on the environment?	No	
1.28	Influx of people to an area in either temporarily or permanently?	No	No residential facilities are envisaged at the project site.
1.29	Introduction of alien species?	No	
1.30	Loss of native species or genetic diversity?	No	
1.31	Any other actions?	No	

2. Use of Natural resources for construction or operation of the Project (such as land, water, materials or energy, especially any resources which are non-renewable or in short supply):

S. No.	Information/checklist confirmation	Yes/ No	Details thereof (with approximate quantities /rates, wherever possible) with source of information data
2.1	Land especially undeveloped or agricultural land (ha)	No	The proposed project is an expansion and will be located within the same plot, no additional land is required.
2.2	Water (expected source & competing users) unit: KLD	Yes	Borewell & from recycled/ recovered effluent, 711 m3/d.
2.3	Minerals (MT)		No

2.4	Construction material – stone, aggregates, sand / soil (expected source – MT)	Yes	Construction materials, like steel, cement, crushed stones, sand, rubble, etc. required for the project shall be procured from the local market. Approx. quantities are as under: Steel – 1800 MT, Cement – 400000 MT Coarse & fine aggregates – 6000 MT
2.5	Forests and timber (source – MT)	No	Mainly Iron / Aluminium/ PVC – Doors & Window frames shall be used. Timber, if required, will be procured from local market.
2.6	Energy including electricity and fuels (source, competing users) Unit**:** fuel (MT), energy (MW)	Yes	• Proposed contract demand: 2517 KVA, Madhya Gujarat Vij Company Limited. • DG,1 *600 KVA & 2*1010 KVA as stand by • HSD: 480 kg/hr
2.7	Any other natural resources (use appropriate standard units)		Addl Furnace oil for proposed expansion: 1078 kg/hr for boiler & TFH

3. Use, storage, transport, handling or production of substances or materials, which could be harmful to human health or the environment or raise concerns about actual or perceived risks to human health.

S. No.	Information/Checklist confirmation	Yes/ No	Details thereof (with approximate quantities/rates, wherever possible) with source of information data
3.1	Use of substances or materials, which are hazardous (as per MSIHC rules) to human health or the environment (flora, fauna, and water supplies)	Yes	Kindly refer **Annexure – 3**.
3.2	Changes in occurrence of disease or affect disease vectors (e.g. insect or water borne diseases)	No	
3.3	Affect the welfare of people e.g. by changing living conditions?	Yes	• In proposed expansion there will be manufacturing of bulk drugs and bulk drug intermediates which is raw material for manufacturing drugs for treatment of disease. • Generation of additional employment • Contribution to country's revenue generation.
3.4	Vulnerable groups of people who could be affected by the project e.g. hospital patients,	Yes	Positive indirect impact due to manufacturing of new / cost effective

	children, the elderly etc.,		drugs / drug intermediates for treatment of disease. Also refer S. No. 3.3
3.5	Any other causes	No	

4. Production of solid wastes during construction or operation or decommissioning (MT/month)

S. No.	Information/Checklist confirmation	Yes/ No	Details thereof (with approximate quantities/ rates, wherever possible) with source of information data
4.1	Spoil, overburden or mine wastes	No	
4.2	Municipal waste (domestic and or commercial wastes)	Yes	Canteen waste will be generated which will be used for vermi-composting.
4.3	Hazardous wastes (as per Hazardous Waste Management Rules)	Yes	Kindly refer **Annexure – 4.**
4.4	Other industrial process wastes	No	**-**
4.5	Surplus product	No	
4.6	Sewage sludge or other sludge from effluent treatment	No	Kindly refer **Annexure – 4.**
4.7	Construction or demolition wastes	Yes	Excavated material will be used in leveling & landscaping. Recyclable material like metal/ plastic will be sold to recyclers.
4.8	Redundant machinery or equipment	No	
4.9	Contaminated soils or other materials	No	
4.10	Agricultural wastes	No	
4.11	Other solid wastes	Yes	Boiler ash, insulation waste, cooling tower fins, packing material, cardboards, thermocol, paper, etc.

5. Release of pollutants or any hazardous, toxic or noxious substances to air (Kg/hr)

S. No.	Information/Checklist confirmation	Yes/ No	Details thereof (with Approximate quantities/ rates, wherever possible) with source of information data
5.1	Emissions from combustion of fossil fuels from stationary or mobile sources	Yes	Adequate stack height as per CPCB norms will be provided to meet: PM – 150 mg/Nm3

			SO2 – 100 ppm NOx – 50 ppm
5.2	Emissions from production processes	Yes	Pollutants include HCl & NH_3. HCl – 20 mg/Nm^3 NH3 – 175 mg/Nm^3 Vents will be connected to scrubber before discharge to meet prescribed limit.
5.3	Emissions from materials handling including storage or transport	Yes	Certain bulk storage tanks having volatile solvents shall be provided with either insulations or vent chillers to prevent emissions.
5.4	Emissions from construction activities including plant and equipment	Yes	Intermittent & insignificant emissions limited to construction phase only.
5.5	Dust or odours from handling of materials including construction materials, sewage & waste	No	Intermittent dust generation expected during construction phase only.
5.6	Emissions from incineration of waste	No	Waste generated will be sent to common TSDF.
5.7	Emissions from burning of waste in open air (e.g. slash materials, construction debris)	No	
5.8	Emissions from any other sources	No	

6. Generation of Noise and Vibration, and Emissions of Light and Heat:

S. No.	Information/Checklist confirmation	Yes/ No	Details thereof (with approximate quantities/ rates, Wherever possible) with source of information data
6.1	From operation of equipment e.g. engines, ventilation plant, crushers	No	All DG sets will be provided with acoustic enclosures to minimize noise level. DG sets are stand-by.
6.2	From industrial or similar processes	Yes	Noise area includes utilities like air compressor rooms etc. This shall be located in isolated area as far as possible. Besides, personal protective equipment shall be used with restricted people movement.
6.3	From construction or demolition	Yes	Insignificant and limited during construction period.
6.4	From blasting or piling	No	
6.5	From construction or operational traffic	Yes	Intermittent and limited to construction in day time only.
6.6	From lighting or cooling systems	No	

6.7	From any other sources	No	

7. Risks of contamination of land or water from releases of pollutants into the ground or into sewers,
surface waters, groundwater, coastal waters or the sea:

S. No.	Information/Checklist confirmation	Yes/ No	Details thereof (with approximate quantities/rates, wherever possible) with source of information data
7.1	From handling, storage, use or spillage of hazardous materials	No	All major storage areas shall have impervious flooring & dykes.
7.2	From discharge of sewage or other effluents to water or the land (expected mode and place of discharge)	No	Sewage will be treated along with industrial effluent & treated effluent shall be discharged to CETP and/ or reuse.
7.3	By deposition of pollutants emitted to air into the land or into water	No	As pollutants will be scrubbed before discharge in to air.
7.4	From any other sources	No	
7.5	Is there a risk of long term build up of pollutants in the environment from these sources?	No	

8. Risk of accidents during construction or operation of the Project, which could affect human health or the environment

S. No.	Information/Checklist confirmation	Yes/ No	Details thereof (with approximate quantities/rates, wherever possible) with source of information data
8.1	From explosions, spillages, fires etc from storage, handling, use or production of hazardous substances	No	Necessary arrangement including fire / smoke detection, fire alarm, fire hydrant systems, spill control kit, shall be made.
8.2	From any other causes	No	
8.3	Could the project be affected by natural disasters causing environmental damage (e.g. floods, earthquakes, landslides, cloudburst etc)?	No	Adequate structural design to withstand earthquake considering seismicity of the area (Zone III) Storm water drainages of adequate capacity shall be provided.

9. Factors which should be considered (such as consequential development) which could lead to environmental effects or the potential for cumulative impacts with other existing or planned activities in the locality

S. No.	Information/Checklist confirmation	Yes/ No	Details thereof (with approximate quantities/rates, wherever possible) with source of information data

9.1	Lead to development of supporting. lities, ancillary development or development stimulated by the project which could have impact on the environment e.g.**:** • Supporting infrastructure (roads, power supply, waste or waste water treatment, etc.) • Housing development • Extractive industries • Supply industries • Other	Yes	Project will stimulate infrastructure development of Village – Dabhasa
9.2	Lead to after-use of the site, which could havean impact on the environment	No	
9.3	Set a precedent for later developments	Yes	
9.4	Have cumulative effects due to proximity to other existing or planned projects with similar effects	No	

(III) Environmental Sensitivity

S.No.	Areas	Name/ Identity	Aerial distance (within 15 km.) Proposed project location boundary
1	Areas protected under international conventions, national or local legislation for their ecological, landscape, cultural or other related value	No	No such areas exist within 15 km. Current Expansion is located 15.7 km from Vadodara and 4.4 km from Padra region
2	Areas which are important or sensitive for ecological reasons - Wetlands, watercourses or other water bodies, coastal zone, biospheres, mountains, forests	Yes	Only water bodies exist within 15 kms as covered in Point No. 4 below:
3	Areas used by protected, important or sensitive species of flora or fauna for breeding, nesting, foraging, resting, over wintering, migration	Yes	Few migratory birds (e,g. Rosy, Pastor) are occasionaly observed in the area.
4	Inland, coastal, marine or underground waters	Yes	MahisagarRiver; Padra Pond Dabhasa Pond
5	State, National boundaries	No	Not Applicable
6	Routes or facilities used by the public for access to recreation or other tourist, pilgrim areas	No	Not Applicable
7	Defence installations	None	Not Applicable
8	Densely populated or built-up area	No	
9	Areas occupied by sensitive man-made land uses *(hospitals, schools, places of worship,*	Yes	Dabhasa School Dabhasa Temple

	community facilities)		
10	Areas containing important, high quality or scarce resources *(ground water resources, surface resources, forestry, agriculture, fisheries, tourism, minerals)*	None	Not Applicable
11	Areas already subjected to pollution or environmental damage. *(Those where existing legal environmental standards are exceeded)*	No	
12	Areas susceptible to natural hazard which could cause the project to present environmental problems (*earthquakes, subsidence, landslides, erosion, flooding or extreme or adverse climatic conditions*)	No	The area falls under Sesmic Zone – III. All structures will be designed considering the sesmic zone of the area.

(IV). Proposed Terms of Reference for EIA studies: –

I hereby given under taking that the data and information given in the application and enclosure are true to the best of my knowledge and belief and I am aware that if any part of the data and information submitted is found to be false or misleading at any stage, the project will be reject and clearance give, if any to the project will be revoked at our risk and cost.

For LUPIN LIMITED

AUTHORISED SIGNATORY

Date: 14.09.15
Place: Dabhasa

Signature of the applicant
With Name and Full Address
(Project proponent / Authorised Signatory)

Annexure - 1

Products and Production Capacities

Existing and proposed production capacities are given as under:

List of Products with Production capacities

List & Quantum of Production for Environmental Clearance			
Group	**S. No**	**Name Of Proposed Product List**	**Proposed Production (T/A)**
A		Category : I	800
	1	1-(3-Chlorophenyl)-4-(3-Chloropropyl) Piperazine Hydrochloride	
	2	4-Chlorobenzhydryl Piperazine	
	3	4-Chlorobenzhydryl Chloride	
	4	4-Chlorobenzhydrol	
	5	2-Benzhydrylsulphinyl Acetic Acid	
	6	S-(+)-2-Aminobutyramide Hydrochloride	
B		Category : II	200
	7	1-Amino Indane	
	8	Lacosamide	
	9	Imino Rifamycin-S	
	10	Amisulpride	
	11	Flupirtine Maleate	
	12	Quetiapine Fumarate	
	13	Atorvastatin Calcium	
	14	Simvastatin	
	15	Desvenlafaxine Succinate	
	16	Desvenlafaxine Benzoate	
	17	Prasugrel Hydrochloride	
	18	Ilaprazole	
	19	Eslicarbazepine Acetate	
	20	Fenofibrate	
	21	Aripiprazole	
C		Category : III	300
	22	Levetiracetam	
	23	Ranolazine	
	24	Duloxetine Hydrochloride	
	25	Irbesartan	
	26	Venlafaxine Hydrochloride	
	27	Pantoprazole Sodium Sesquihydrate	
	28	Amlodipine Besylate	
	29	Levofloxacine Hemihydrate	
	30	Esomeprazole Magnesium	
	31	Pregabalin	
	32	Olmesartan Medoxomil	
	33	Candesartan Cilexetil	

List & Quantum of Production for Environmental Clearance			
Group	**S. No**	**Name Of Proposed Product List**	**Proposed Production (T/A)**
	34	Iloperidone	
	35	Febuxostat	
	36	Proglumetacin Maleate	
	37	Nimorazole	
	38	Entacapone	
	39	Itopride Hydrochloride	
	40	Etiracetam	
	41	Efletirizine	
	42	Carvedilol	
	43	Rasagiline Mesylate	
	44	Pramipexole Dihydrochloride	
	45	Flupirtine Base	
	46	Trimethobenzamide Hydrochloride	
	47	Fasudil Hydrochloride	
	48	Ramosetron Hydrochloride	
	49	Lurasidone Hydrochloride	
	50	Cicletanine Hydrochloride	
	51	Celecoxib	
	52	Omeprazole	
D		Category : IV	80
	53	Clopidogrel Bisulfate	
	54	Desloratadine	
	55	Sevelamer Carbonate	
	56	Clindamycin Palmitate Hydrochloride	
	57	Armodafinil	
	58	Azithromycin Monohydrate	
	59	Lansoprazole	
	60	Diacereine	
	61	Memantine Hydrochloride	
	62	Eszopiclone	
	63	Tolterodine Tartrate	
	64	Dronedarone Hydrochloride	
	65	Fexofenadine Hydrochloride	
	66	Trazodone Hydrochloride	
	67	Conivaptan Hydrochloride	
	68	Mirabegron	
	69	Efavirenz	
	70	Telmisartan	
	71	Pioglitazone Hydrochloride	
	72	Emtricitabine	
	73	Mesalamine	

List & Quantum of Production for Environmental Clearance			
Group	**S. No**	**Name Of Proposed Product List**	**Proposed Production (T/A)**
	74	Ziprasidone Hydrochloride	
	75	Bazedoxifene Acetate	
	76	Rabeprazole Sodium	
	77	Naftopidil	
	78	Tenofovir Disoproxil Fumarate	
	79	Ritonavir	
E	80	R & D Pilot Plant Trial Run Products (Bulk Drugs and Intermediates)	100
Total Quantity of Proposed Production			**1480**

List of Proposed By-products

S. No	Name Of Proposed By-Product List	Quantity (T/A)
1	Ammonium Sulphate	415
2	Sodium Salts (NaBr, NaCl, Na2SO3)	3634
3	Piperazine Liquor	68
4	Potassium Salts (KBr, KCl)	1567
5	Diammonium Tartarate	928
6	Acetic acid	158
7	Palmitic acid	89
	Total	**6858**

List and Quantum of Production of Existing CCA

List & Quantum of Production of Existing CCA			
Group	**S.No**	**Name Of Existing Product List**	**Existing Production (T/A)**
A		Category : I	140
	1	1-(3-Chlorophenyl)-4-(3-Chloropropyl) piperazine hydrochloride	
	2	N-(4-Chlorobenzhydryl) Piperazine	
	3	1-Amino Indane	
	4	4-chloro-benzhydrylchloride	
	5	Para-chlorobenzhydrol	
	6	Imino Rifamycin	
	7	2-Benzhydrylsulphinylacetic acid	
B		Category : II	340
	8	S-(+)-2-Aminobutyramide Hydrochloride	
	9	Levetiracetam	
	10	Flupirtine Maleate	
	11	Eslicarbazepine acetate	
C		Category : III	91.4
	12	Quiteapine Fumerate	
	13	Armodafinil	
	14	Ranolizine	
	15	Duloxitine	
	16	Atorvastatin	
	17	Sertraline Hydrochloride	
	18	Lansoprazole	
	19	Venlafaxin	
	20	Pentaprazole	
	21	Amlodipine Besylate	
	22	Azythromycin	
	23	Fenofibrate/Choline Fenofibrate	
	24	Levofloxacin	
	25	Memantine HCl	
	26	Esomeprazole Magnesium	
	27	Mesalamine	
	28	Eszopiclone	
	29	Tolterodine Tartrate	
	30	Simvastatin	
	31	Pregabalin	
	32	Desvenlafaxine Benzoate-Succinate	
	33	Olmesartan	
	34	Candesartan	

List & Quantum of Production of Existing CCA			
Group	**S.No**	**Name Of Existing Product List**	**Existing Production (T/A)**
	35	Iloperidone	
	36	Lacosamide	
	37	Febuxostat	
	38	Dronedarone	
	39	Prasugrel	
	40	Nimorazole	
	41	Fexofenadine	
	42	Aripiprazole	
	43	Entacapone	
	44	Itopride	
	45	Trazadone	
	46	Etiracetam	
	47	Rivastigmine	
	48	Efletrizine	
	49	Rasagiline	
	50	Conivaptan	
	51	Pramipexol	
	52	Illaprazole	
	53	Flupirtine Gluconate	
	54	Trimethobenzamide	
	55	Fasudil	
	56	Ramosetron	
	57	Lurasidone	
	58	Cicletanine	
	59	Celecoxib	
	60	Rabeprazole	
	61	Acotiamide	
	62	Omperazole	
	63	Sevelamer Carbonate	
	64	Bepotastine	
	65	Nelatenxine	
	66	Revaprazan	
D	67	R & D Pilot Plant Trial Run Products (Bulk Drugs and Intermediates)	24
Total Quantity of Existing Production			**595.4**

List of Existing By-products

S.No	Name Of Existing By-Product List	Quantity (T/A)
1	Piperazine Derivatives	37.94

2	Sodium / Potassium Salts	618.69
3	Ammonium Salts	25
Total		**681.63**

Process Description

Process Brief

The manufacturing of bulk drugs and bulk drug intermediates involves several unit operations and processes. It involves several stages of reactions in which different functional groups are attached to the starting key raw materials. The product formed after each stages of reaction are called as intermediates. In most of the cases the downstream processing of the reaction mixture such as filtration, distillation etc. is also conducted prior to the next reaction step. The final reaction mixture goes through multiple steps of downstream processing to produce the desired active product in solid form. These steps include filtration, distillation, precipitation, crystallization, drying, milling and final packing.

Reaction

Raw materials or ingredients, including solvents, used to produce the intermediates or bulk drug substances are charged into the reactor vessel. Raw materials are charged into the reactor which includes solids and liquids. If solvents are used then the reaction mixture is inertise.

The reactors are attached to the double process condensers (primary and secondary) to recover solvents from process operations. They are also attached to the air pollution control measures like scrubbers, if required.

The spent solvent goes for in-house solvent recovery plant for recovery and reuse or disposal to authorized party.

Separation

It involves several mechanisms like extraction, decanting, centrifugation and filtration. These mechanisms are employed jointly or individually, in multiple stages to separate the intermediates or bulk drug substance from the reaction solution and to remove impurities.

Crystallization is also used to separate the desired intermediates or API from the reaction solution.

Purification

Once the intermediate or bulk drug substance has been separated, it may need to be purified. Purification is carried out by re-crystallization or washing with additional solvents and filtration.

Drying & Powder Processing

The various types of drying equipment used are rotary vacuum dryers (RVD), agitated nutsche filter dryer (ANFD) and fluidized bed dryer (FBD) etc. depending upon the process. The dried powder undergoes milling and micronisation operation to get the desire particle size of the product.

A brief process description for all products is as listed below:

PROCESS DESCRIPTION

1. **1-(3-CHLOROPHENYL)-4-(3-CHLOROPROPYL)PIPERAZINE HYDROCHLORIDE [T2 HCl]**

   m-Chloroaniline is reacted with BIS HCl in presence of base in water to give crude T1. Pure T1 is obtained after fractional distillation. Pure T1 is reacted with 1-bromo-3-chloropropane in presence of caustic lye in water and after workup obtained 1-(3-chlorophenyl)-4-(3-Chloropropyl) Piperazine Hydrochloride (T2.HCl) by adjusting pH with Con. HCl.

2. **4-CHLOROBENZHYDRYL PIPERAZINE [PCBHP]**

   PCBP reacts with Sodium borohydride in presence of Cat-D and water is used for reaction, followed by work-up in Toluene and org.layer of PCBH insitu taken for PCBHC preparation by using HCl gas (generated from Con. HCl + Con. H2SO4) followed by water washing and Toluene recovery to get crude PCBHC. Crude PCBHC converted to PCBHP using Anhy. Piperazine and Toluene as a solvent followed by isolation of PCBHP in water.

3. **4-CHLOROBENZHYDRYL CHLORIDE [PCBHC]**

   PCBP reacts with Sodium borohydride in presence of Cat-D and water is used for reaction, followed by work-up in Toluene and org.layer of PCBH insitu taken for PCBHC preparation by using HCl gas, (generated from Con. HCl + Con. H2SO4) followed by water washing and Toluene recovery to get crude PCBHC. PCBHC crude and on distillation it gives pure 4-Chlorobenzhydryl Chloride (PCBHC).

4. **4-CHLOROBENZHYDROL [PCBH]**

   PCBH prepared from PCBP by using Sodium borohydride in presence of Cat-D and water is used for reaction, and final product isolated in Hexane.

5. **2-BENZHYDRYLSULPHINYL ACETIC ACID [2-BSAA]**

   2-BSAA prepared from 2-Diphenyl Methyl Thio Acetic acid [MDL-1] by using H_2O_2 and Acetic acid as a solvent followed by isolation of 2-BSAA crude by water addition. Crude 2-BSAA treated with MeOH in presence of TEA to get Methanol base 2-BSAA further it purified by acid base treatment to get pure 2-Benzhydrylsulphinyl acetic acid [2-BSAA].

6. **S-(+)-2-AMINOBUTYRAMIDE HYDROCHLORIDE [SABAM HCL]**

   Methyl-2-bromobutyrate is converted to RSABAM HBr in autoclave with using Ammonia pressure & Methanol as a solvent.

RSABAM.HBr converted into free base using Potassium carbonate in Methanol after removing salt by filtration gives RSABAM base.

Resolution of RSABAM base using L (+) Tartric acid in methanol gives tartrate salt, SABAM TA.

SABAM HCl is obtained from SABAM TA after breaking of SABAM tartrate salt in Methanol using ammonia followed by removing DAT and acidification with IPA HCl.

7. 1-AMINO INDANE [AI]

The 1-Indanone is hydrogenated in Methanol in presence of Ammonia and raney nickel, afterwards filtered the catalyst and distilled the methanol to get 1-Amino indane (crude), which upon purification with caustic and HCl gives pure 1-Amino Indane.

8. LACOSAMIDE

D-serine reacts with Di-tert-butyl-di-carbonate in presence of sodium hydroxide gives N-protected (R)-2-(tert-butoxy carbonyl amino)-3-hydroxy propanoic acid. (Laco-1- Insitu).

(R)-2-(tert-butoxy carbonyl amino)-3-hydroxy propanoic acid reacts with dimethyl sulphate and sodium hydroxide in presence of hydrochloric acid and methylene dichloride gives (R)-2-(tert-butoxy carbonyl amino)-3-methoxy propanoic acid.(Laco-2- Insitu).

(R)-2-(tert-butoxy carbonyl amino)-3-methoxy propanoic acid reacts with benzyl amine, ethyl chloro formate, N- methyl morphaline in presence of hydrochloric acid and methylene dichloride gives (R)-tert-butyl 1-(benzyl amino)-3-methoxy-1-oxopropan-2-ylcarbamate.(Laco-3-- Insitu).

(R)-tert-butyl 1-(benzyl amino)-3-methoxy-1-oxopropan-2-ylcarbamate on treatment with dichloro methane in presence of hydrochloric acid, sodium hydroxide and water gives deprotected (R)-2-amino-N-benzyl-3-methoxypropanamide.(Laco-4-- Insitu).

(R)-2-amino-N-benzyl-3-methoxypropanamide on acetylation with acetic anhydride in presence of dichloro methane and ethyl acetate gives (R)-2-acetamido-N-benzyl-3-methoxypropanamide (LACOSAMIDE).

9. IMINO RIFAMYCIN-S

Amino Rifamycin prepared from Rifamycin S / S-1 using formamide, sodium azide, catalyst Ammonium persulphate (APS) and Chloroform , finally isolation of Amino Rifamycin after Acetic acid recovery followed by addition of 2-methoxy ethanol and washed with Diisopropyl ether.

Amino Rifamycin converted to Imino Rifamycin-S (4-Imino-3-Amino Rifamycin-S) in presence of ammonia gas and Tetrahydrofuran as a solvent. Finally isolation of the product after recovery of THF followed by isolation in 2-Methoxy Ethanol and washed with Water.

10. AMISULPRIDE

4-amino- 2-methoxy-5-ethyl thio methyl benzoate is hydrolyzed by using NaOH solution in methanol; followed by precipitation of material using dil. HCl to prepare thio compound.

4-Amino -2-Methoxy -5-Ethyl thio Benzoic Acid (Thio Compound) is oxidized using H_2O_2 in presence of methanol and Sodium Tungstate Dihydrate as a catalyst to get AMS-I.

AMS-I is condensed with N-Ethyl-2-amino methyl pyrrolidine using triethyl amine and ethyl chloroformate to get Amisulpride crude

Amisulpride crude is purified by crystallization using Acetone to get Amisulpride.

11. FLUPIRTINE MALEATE

If 2-Amino-6-chloro-3-nitropyridine (ACNP) is failing in single impurity purification is done by IPA.

2-Amino-6-chloro-3-nitropyridine reacts with 4-fluorobenzyl amine in presence of triethyl amine in IPA gives 2-Amino-6-(4-fluorobenzylamino)-3-nitropyridine (ANFP).

ANFP reacted with hydrazine hydrate in presence of raney Ni and TBAB to give diamine (AFBP), Ethyl chloroformate is added to form flupirtine hydrochloride. Flupirtine hydrochloride reacts with maleic acid water and IPA to produce flupirtine maleate (Crude).

Flupirtine maleate (Crude) is purified from methanol to furnish Flupirtine maleate (NV01).

12. QUETIAPINE FUMARATE

Dibenzo is converted to its imino chloride (QT-I) using phosphorous oxychloride, which is further condensed with 1-[2-(2-hydroxyethoxy)ethyl]piperazine (HEEP) in the presence of sodium carbonate to obtain Quetiapine base.

The Quetiapine base is then converted to its fumarate salt using fumaric acid in ethanol. Ethanol denatured with toluene has been used in the process.

13. ATORVASTATIN CALCIUM

Methanolic ammonia is prepared by purging ammonia gas in methanol. Cyano derivative is hydrogenated at pressure to amine in presence of Raney Nickel in methanolic ammonia. After the completion of reaction, reaction mass is filtered off through hyflow bed & the filtrate is distilled off completely under vacuum. It is then stripped off with Cyclohexane to obtain as thick oil (ATR- 1).

Amine (ATR-1) is then condensed with Diketo compound in presence of Pivalic acid and cyclohexane, reaction mixture is cooled, ethyl acetate is added and it is washed with sodium Bicarbonate solution. Organic layer after water wash is distilled off. The residual mass is stripped off with Isopropyl alcohol. The mass is then taken in Isopropyl alcohol. To that DM water is added and stirred and filtered. The wet solid is washed with mixture of Isopropyl alcohol and DM water.The solid is dried to give ATR-2.

ATR-2 is deprotected with dil. Hydrochloric acid in Isopropyl alcohol to give Diol Ester. Neutralized the reaction mass with liq. ammonia and then to the reaction mass of Diol Ester in IPA is distilled under reduced pressure. To this concentrated mass methanol is added and mixture is heated to get clear solution. DM water is added for precipitation. Product is then filtered off washed by IPA, DM water and dried.

Water solution of Sodium Hydroxide is added to the mixture of Methanol, ter-butyl methyl ether and diol ester. Reaction mass is the heated and maintained till completion of reaction. After reaction is completed reaction mass is cooled and washing of ter-butyl methyl ether is given. pH is adjusted with HCl solution. Reaction mass is then heated and Solution of Calcium acetate is added to above reaction mass with simultaneously seeding of Atorvastatin calcium trihydrate to get required polymorph. Mixture is then heated and filtered. product is dried under vacuum.

ATR-4 is dissolved in mix. of methyl ethyl ketone & methanol followed by micron filtration. The solution is evaporated using ATFD method, collected product is dried followed by micronization or milling and dried to get Atorvastatin calcium.

14. SIMVASTATIN

Lovastatin is hydrolyzed with alcoholic KOH followed addition of tert-butyl dimethylsilyl chloride (TBMDSi) to obtain THL. THL is acylated with 2,2-Dimethylbutryl chloride (DMBC) followed by deprotection of 4-Hydroxy group and opening of lactone to convert simvastatin acid (an intermediated form) to in Simva ammonium salt by using ammonia. Ammonium salt of Simvastatin is latonized to get Simvastatin S1. Simvastatin S1 goes under purification to form Simvastatin S2 in Cyclohexane in presence of TEA. Simvastatin S2 is further goes under purification to form Simvastatin.

15. DESVENLAFAXINE SUCCINATE

The process involves the demethylation of Venlafaxine Hydrochloride using 2-Diethyl amino ethane thiol Hydrochloride as demethylating reagent, Dimethyl sulfoxide as solvent and Sodium Hydroxide as Base. After the completion of reaction, the reaction mass is quenched with water. The aqueous layer is washed with Toluene. The pH is adjusted with Conc. HCl and filtered through Hyflow. The aqueous layer is washed with Dichloromethane, and thereafter the pH is adjusted with aqueous ammonia. The slurry is stirred and filtered. The wet solid is purified by acid base work up and dried u/v to give Desvenlafaxine Base.

The Desvenlafaxine Base is taken in Acetone & Water, further adding succinic acid. The reaction mass is heated and the subsequently cooled under stirring condition. The acetone & water are again added and the solvent mixture is cooled. The solid product is filtered through carbon-hyflow bed to get pure Desvenlafaxine succinate.

16. DESVENLAFAXINE BENZOATE

The process involves the demethylation of Venlafaxine Hydrochloride using 2-Diethyl amino ethane thiol Hydrochloride as demethylating reagent, Dimethyl sulfoxide as solvent and Sodium Hydroxide as Base. After the completion of reaction, the reaction mass is quenched with water. The aqueous layer is washed with Toluene. The pH is adjusted with Conc. HCl and filtered through Hyflow. The aqueous layer is washed with Dichloromethane, and thereafter the pH is adjusted with aqueous ammonia. The slurry is stirred and filtered. The wet solid is purified by acid base work up and dried u/v to give Desvenlafaxine Base.

Desvenlafaxine Benzate is subsequently formed by heating the Desvenlafaxine Base with Benzoic acid in Isopropyl alcohol and then cooling the reaction mass. The slurry is stirred and filtered to give Desvenlafaxine Benzoate.

17. PRASUGREL HYDROCHLORIDE

Prasugrel prepares by reaction of Oxo-compound with LARM-67 to produce LA67-01 which further reacts with acetic anhydride to form LA67-02. LA67-02 is acidified to form HCl compound (LA67-03). The HCl compound reacts with Halo compound to form LA67-04, in presence of trimethyl amine. LA67-04 is purified with Methanol to form crude material. Hydrochloric acid is charged alongwith Acetone and reacts to form final purified product salt, Prasugrel Hydrochloride.

18. ILAPRAZOLE

CALDIN (5- amino-1H-benzimidazole-2- thiol) is condensed with Dimethoxy tetra hydro furan (DMTHF) in Aq. Acetic acid / methanol media to produce LA70-01. The material is made free from excess acidity and is then dried. The dried material is used as such for the next step.

LA70-01 is reacted with CMP (Chloro Methoxy Pyridine) in MeOH / NaOH mixture to synthesize LA70-02. The material is made free from NaCl and stripped of solvent. Then it is dried. The dried material is used as such for the next step.

Per Acetic Acid (PAA) is added (either neat or a mixture with MDC) into a chilled heterogeous mixture of LA 70-02, MDC, methanol and water. The crude product is isolated by (a) quenching excess PAA (b) washing off excess inorganic salts by water (c) removal of unreacted LA 70-02 by extraction into organic medium at high pH (d) Extraction of LA70 in MDC at neutral pH & precipitation of LA 70 crude from Ethyl acetate followed by MDC evaporation.

Ilaprazole is purified from acetone by dissolution, removal of insoluble material and then crystallization from acetone.

19. ESLICARBAZEPINE ACETATE

Oxcarbazepine is reduced to ES-1 by using Sodium borohydride in water under basic condition.

ES-1 is taken for resolution by using Diacetyl salt of L (+) Tartaric acid in MDC under phase transfer condition to make ES-2 (wet).

ES-2 (wet) is directly taken for hydrolysis by using caustic lye to make ES-3.

ES-3 is acetylated by using acetic anhydride/TEA in MDC. Eslicarbazepine acetate (ES-10) is crystallized from IPA.

20. FENOFIBRATE

Hydroxy compound ((4-chlorophenyl)(4-hydroxyphenyl) methanone) is reacted with acetone and chloroform in presence of sodium hydroxide at reflux temperature to get fenofibric acid. (FF-I).

FF-I is then converted into its isopropyl ester under reflux condition in presence of sulfuric acid to yield Fenofibrate i.e. (Isopropyl 2-(4-(4-chlorobenzoyl) phenoxy) 2-methylpropanoate).

21. ARIPIPRAZOLE

A suspension of DCP (1-(2,3-dichlorophenyl)piperazine) Hydrochloride and DBB (1-4-Dibromobutane) is made in water and then allowed to react at refluxing temperature in presence of excess Potassium carbonate. The crude intermediate obtained at this stage by partial condensatin of DCP and DBB is separated out and then solidified by addition of acetone.

The pure intermediate I and 7-Hydroxy Carbostyryl are suspended in xylene and excess potassium carbonate is charged. The resulting hetrogenous mixture is refluxed to complete the reaction. The crude product is isolated by distillation under vacuum followed by addition of water to dissolve away potassium salts. The solid product obtained at this stage is used as such in the next step.

The crude product is dissolved in toluene and carbon is added. Refluxing, filtration, cooling, filtration and drying provides solid pure product.

22. LEVETIRACETAM

SABAM Hydrohcloride & 4-Chlorobutanoyl chloride (4-CBC) is condensed in presence of tetrabutyl ammonium bromide and sodium sulfate in MDC to form condensed product which

is further cyclised using potassium hydroxide to give Leve-I. Leve-I is purified in ethylacetate to get Levetiracetam.

23. RANOLAZINE

Condensation of 2,6-Xylidine and Chloro acetyl chloride in acetone and water mixture as solvent under basic condition is done. After completion of reaction, precipitations of Chloro acetamide is accomplished by adding water to the reaction mass, whereby solid precipitates out. Isolation of Chloro acetamide compound is done by filteration of solid followed by slurry wash of wet cake with water and acetone (chilled) respectively followed by drying under reduced pressure.

Anhydrous Piperazine reacts with Chloro acetamide in Isoproyl alcohol as solvent. After completion of reaction, the reaction mass is cooled to room temperature and the Isopropyl alcohol is removed under reduced pressure. A large quantity of water is added to concentrated solid slurry mass. Aqueous mass is acidified using acetic acid and aqueous mass so obtained is then washed with dichloromethane to remove Dimer impurity. Thereafter, aqueous mass is basified and extracted with dichloromethane. Organic layer is washed with water and brine respectively. Concentration of Organic layer under reduced pressure and subsequent addition of Cyclohexane results in isolation of solid mass. Slurry mass is filtered, wet cake washed with cyclohexane and after suck drying, the cake is further dried under reduced pressure to get white crystalline solid as Piperazine acetamide.

Condensation of 2-methoxy phenol with epichlorohydrin is carried under basic reaction condition. After completion of the reaction, and subsequently workup concentrate the oily mass under reduced pressure, oily mass is taken forward for next stage as such without further purification.

Condensation of Piperazine acetamide and epoxide compound in Toluene and Methanol solvent mixture is done under Nitrogen atmosphere. After completion of the reaction and subsequently work up concentration of the combined organic layer under reduced pressure affords the oily mass and addition of solvents to oily mass results in isolation of precipitates. Slurry mass is filtered, wet cake washed with solvents and after suck drying of the wet cake, solid is further dried under reduced pressure to get white solid as Ranolazine Base crude.

Crude Ranolazine is subjected to purification to improve the color and improve the RS purity of the salt.

24. DULOXETINE HYDROCHLORIDE

DTP.HCL (3-(dimethylamino)-1-(thiophen-2-yl)propan-1-one hydrochloride) is reduced with alkali metal Sodium borohydride in methanol and water as a solvent to give Dulox-I

Dulox-I is further reacted with ~~1- naphthalene fluoro-~~1-Fluoronaphthalene in presence of sodamide, in DMSO solvent to give condensed product which is isolated using oxalic acid dihydrate to get, Dulox-II

Dulox-II is made a salt free using aq ammonia, then resolving the compound with Dibenzoyl-L-Tartaric acid monohydrate (DBTA) in ethyl acetate ,methanol to give Dulox-III.

Dulox-III is made salt free using Aq. ammonia, then it is reacted with phenyl chloroformate in presence of DIPEA to give a oily carbomate compound which is further hydrolyzed using sodium hydroxide in DMSO and water to give crude duloxetine (Dulox-IV) which is isolated as a hydrochloride salt using Ethylacetate HCl.

Purification of crude duloxetine HCl (Dulox-IV) is carried out in acetone and methanol mixture to give pure Duloxetine Hydrochloride.

25. IRBESARTAN

Spiro Hydrochloride is converted into spiro free base by using aqueous ammonia solution and extracted in MDC. MDC layer is then concentrated to get residual spiro base.

Residual spiro base is then condensed with BMC in presence of potassium hydroxide as base and DMF as solvent. After reaction completion reaction masss is then quenched with water & crude IRN-I is filtered from reaction mass which is then crystallized with IPA & water resulting into IRN-I.

IRN-I is reacted with sodium azide in presence of TEA HCl and MIBK as solvent resulting into tetrazole ring formation which yielding crude Irbesartan.

Crude Irbesartan is then crystallized with methanol and ethyl acetate to get final Irbesartan

26. VENLAFAXINE HYDROCHLORIDE

4-Methoxy Phenyl Acetonitrile (4-MPACN) was treated with powder sodium hydroxide in methanol followed by slow addition of cyclohexanone. D M water is added in the reaction mass with vigorous stirring. pH of reaction mass is adjusted adding dil hydrochloric acid.

Slurry is stirred and solid is isolated by filtration followed by D M water wash. Purification is carried out in toluene to give 2-Cyano (4-Methoxy Phenyl Methyl) Cyclohexanol (CCH).

2-Cyano (4-Methoxy Phenyl Methyl) Cyclohexanol (CCH) is treated with Raney Nickel under Hydrogen pressure in Methanolic Ammonia to form amine after complete reaction. Raney nickel is filtered. The filtrate is concentrated under reduced pressure. The residual mass is diluted with water and pH adjusted with conc. HCl solution. The reaction mixture is washed with Dichloromethane and pH of aqueous layer is adjusted with NaOH solution. The product is extracted in Dichloromethane . The Dichloromethane layer is washed with disodium EDTA solution. The Dichloromethane layer is concentrated under reduced pressure, the residual mass is diluted with water.

Formic acid and Formaldehyde is added to the residual mass, the reaction mass is heated, cooled & washed with ethyl acetate to remove the pink impurity. The aqueous layer is collected & pH is adjusted with NaOH solution. The product is extracted in ethyl acetate and the ethyl acetate layer is washed with brine solution. The ethyl acetate layer is concentrated under reduced pressure. To the residual mass, isopropanol is added & pH is adjusted by isopropanol HCl and filtered the reaction mass suck dried and dried under vaccum.

Venlafaxine HCl crude purified in IPA by dissolving and recrystallization by cooling and collected solid by filtration and dried under vacuum.

27. PANTOPRAZOLE SODIUM SESQUIHYDRATE

Preparation of CDMP HCl from HMDP by chlorination with using Thionyl chloride. Sulphide compound(Panto-1) is prepared by condensation of CDMP HCl compound with DFMB compound in presence of sodium hydroxide as a base in aqueous methanol. Extracted in MDC & isolated in cyclohexane.

Sulfoxide (Panto-2) is prepared by oxidation of Sulphide compound (panto-1) by using oxidizing reagent (sodium hypochlorite solution). Extracted in MDC & isolated in DIPE.

Pantoprazole sodium sesquihydrate is prepared by treating sulphoxide compound (Panto-2) with sodium hydroxide in alcohol. It is isolated in the mixture of MDC & DIPE.

28. AMLODIPINE BESYLATE

This stage involve, Benzylidine intermediate preparation by condensation of ethyl 4-[2-(1, 3-dioxo-1, 3-dihydro-2H-isoindol-2-yl) ethoxy]-3-oxobutanoate with 2-chloro benzaldehyde in

presence of piperidine & acetic acid as a catalyst. Benzylidine intermediate further reacted with methyl(2E)-3-aminobut-2-enoate in acetic acid to form Phthaloyl Amlodipine.

It involves, preparation of free base of Amlodipine from Methylamine solution with DNS (Denatured with Toluene) as a solvent.

Free Amlodipine is reacted with Benzene sulfonic acid with DNS to form crude Amlodipine besylate.

Purification of Amlodipine Besylate crude with DNS as a Solvent is done to get Amlodipine Besylate.

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29. LEVOFLOXACINE HEMIHYDRATE

This stage involve, Purification of levo ester with acetone.

Hydrolysis of ester to acid with NaOH as a base with THFas a solvent is carried out to get Levo-II.

Condensation of LEVO-II with N-Methyl piperazine in presence of DMSO & DNS is carried out to get Levofloxacine hemihydrate.

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30. ESOMEPRAZOLE MAGNESIUM

2-chloromethyl-4-methoxy 3,5-dimethylpyridine Hydrochloride is condensed with 5-methoxy-1H- benzimidazole-2-thiol in presence of caustic solution using methanol water mixture to get sulfide compound (5-Methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl)sulfanyl]-1H benzimidazole).

Sulfide compound is oxidized by using diluted hydrogen peroxide in presence of ammonium molybdate as catalyst in methanol to give Omeprazole.

Resolution of Omeprazole is carried out using S-Binol in toluene & cyclohexane solvent mixture to give ESOM-I (S-(-)-Binol complex of 5-methoxy-2-{[(4-methoxy3,5-dimethylpyridin-2-yl)methyl]sulfinyl}-1-H-benzimidazole).

ESOM-I is made a binol free by using potassium hydroxide in methanol, then isolated as a magnesium salt using Magnesium sulfate hepta-hydrate in acetone water mixture.

31. PREGABALIN

CMH ((+)-3-(carbamoylmethyl)-5-methyl hexanoic acid) is treated with R-(+)-1 Methyl benzyl amine in chloroform & methanol mixture to obtain R-CMH Salt [R(+)-1-Methylbenzyl amine salt of R (-)-3 (Carbamoylmethyl)-5-methyl hexanoic acid] (step-1) as solid whereas the unwanted salt of (S)-isomer remains in the solution (filtrate-also contains some R(+)-1-Methylbenzyl amine salt of R (-)-3 (Carbamoylmethyl)-5-methyl hexanoic acid).

R (+)-1-Methylbenzyl amine salt of R (-)-3 (Carbamoylmethyl)-5-methyl hexanoic acid is acidified with aqueous sulfuric acid in water to obtain R (-)-3 (Carbamoylmethyl)-5-methyl hexanoic acid) step-2 (R-CMH) as precipitate, which can be dried under vacuum or it can be directly processed as wet mass in to the next stage(Hofmann rearrangement).The R (+)-1-Methylbenzylamine goes in filtrate as sulphate salt.

R (-)-3-(Carbamoylmethyl)-5-methyl hexanoic acid (R-CMH) is reacting with NaOCl solution to undergo Hoffmann reaction and optical inversion to give wet Crude Pregabalin which can be directly purified as wet mass or it can be dried under vacuum.

Crude Pregabalin (Step-3 mass) is purified using aqueous isopropanol to afford Pregabalin.

32. OLMESARTAN MEDOXOMIL

Hydrolysis of OLMT-I i.e [Ethyl-4-(1-Hydroxy-1-methylethyl)-2-propyl-1-{4-[2-(trityltetrazole-5-yl)phenyl} methylimidazole-5-carboxylate] with sodium hydroxide in Isopropyl alcohol as solvent resulting into OLMT-II.

OLMT-II is then reacted with chlorodioxolene (known as 4-chloromethyl-5-methyl-1,3-dioxol-2-one) in presence of potassium carbonate and DMF as solvent to get crude OLMT-III this is then crystallized with acetonitrile and resulted into OLMT-III.

OLMT-III is deprotected with aqueous acetic acid & removed trityl alcohol from reaction mass after complete reaction by filtration. Filtrate is then evaporated by ATFD and residual API crystallized with acetone to get final Olmesartan Medoxomil, which is chemically known as 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-carboxylicacid(5-methoxy- 2 -oxo-1,3-dioxol-4-yl)methylester.

33. CANDESARTAN CILEXETIL

2-ethoxy-7-carboxy-1-(2'-(1H-tetrazol-5-yl)biphenyl-4-yl) methylbenzimidazole methyl ester (CDS2) is hydrolysed to form Candesartan.

Candesartan is reacted with 1-chloroethylcyclohexyl carbonbate in presence of potassium carbonate in DMF to produce candesartan cilexetil.

34. ILOPERIDONE

4-Hydroxy-3-methoxy acetophenone (HMA) & 1-Bromo-3-chloropropane are reacted in presence of Potassium carbonate in acetonitrile using PTC (TBAB). After completion of reaction, excess of solvents and Bromochloro propane are removed by vacuum distillation. The oily product thus obtained is diluted with methanol and isolated the product i.e.Bromo and Chloro ether derivatives (1-[4-(3-Chloro or Bromo-propoxy)-3-methoxyphenyl] ethanone) by precipitating with water.

Reaction of 6-Fluoro-3-(pipridine -4-yl)-1, 2-benzisoxazole hydrochloride (ILO-2) with Br/Cl ether derivative (ILO-2) is done under mild N2 pressure (Inert atmosphere) in a mixture of methanol, potassium carbonate and TBAB. After completion of reaction, methanol is distilled out under vacuum to get solid residue and DM water is added into the residue and then extracted the material with toluene are separated and toluene is distilled and the crude Iloperidone is isolated.

Iloperidone (crude) is leached in methanol and then cooled the reaction mixture and filtered to get semi pure white to off-white crystalline solid Iloperidone semi pure.

Finally semi pure Iloperidone is dissolved in acetone at reflux temp and Charcolized and filter. Cooled the reaction mixture and filtered to get highly pure Iloperidone white to off-white crystalline solid material.

35. FEBUXOSTAT

Ethyl-2-(3-cyano-4-isobutoxyphenyl)-4-methyl-5-thiazolecarboxylate (NV07-3) is hydrolyzed with sodium hydroxide solution in isopropyl alcohol to furnish the product. The pH is adjusted with hydrochloric acid and solid is separated by filtration as Febuxostat crude.

Febuxostat (crude) is dissolved in acetone and charcoalized. After filtration, acetone is distilled out and solid is filtered to give Febuxostat.

36. PROGLUMETACIN MALEATE

Proglumide reacts with 2-[4-(3-chloropropyl) piperazine-1-yl] ethanol dihydrochloride in presence of potassium carbonate in MIBK to produce Intermediate -1. It is isolated as oxalate salt by adding oxalic acid dihydrate.

Intermediate-1 is treated with NaOH and then with indometacin in presence of maleic acid & Dicyclohexylcarbodiimide (DCC) in MDC to give N-[2-[1-(p-chlrobenzoyl)-5-methoxy-2-methyl-3-indolylacetoxy] ethyl]-N'-[3-(N-benzoyl-N',N'-di-n-propyl-DL-isoglutaminyl) oxypropyl] piperazine (±)-dimaleate (Proglumetacin maleate crude).

Proglumetacin maleate crude is purified using methanol to give proglumetacin maleate semipure.

Proglumetacin maleate semipure is purified with methanol: water to give Proglumetacin maleate.

37. NIMORAZOLE

4-Nitroimidazole in methanol is reacted with sodium hydroxide to make sodium salt of 4-nitroimidazole. Excess methanol and the water generated in the process are stripped out using toluene.

4-(2-Chloroethyl) morpholine hydrochloride in D M water is adjusted to pH by using sodium carbonate solution. Free base of 4-(2-chloroethyl) morpholine thus generated is extracted with toluene .

A suspension of Na- 4-Nitroimidazole & 4-(2-Chloroethyl) morpholine are allow to react in toluene. NaCl generated is filtered off and then toluene is distilled out from the solution. The residual mixture of product and the isomer is crystallised from aqueous methanol to provide the pure Nimorazole

38. ENTACAPONE

The condensation of 3, 4-dihydroxy-5-nitrobenzaldehyde (DHNB) and 2-cyano-N-N-diethyl acetamide (DECA) to make crude Entacapone is carried out using ethanol as a solvent and Morpholine acetate as a catalyst. The crude product is obtained by removal of solvent followed by addition of water. The crude product is dried.

Purification of the crude Entacapone to obtain pure product is done by crystallization from acetic acid containing trace of HBr. The finished product pure Entacapone is obtained by filtration followed by washing with toluene and drying.

39. ITOPRIDE HYDROCHLORIDE

Verateric acid and Thionyl Chloride is reacted in toluene medium in presence of DMF. At the end of the reaction any excess of thionyl chloride is removed by purging nitrogen in the solution. The crude VC (Vertroyl Chloride) obtained is used as such in the next step.

ITO ((2-[4 - aminomethyl) phenoxy] N,N-dimethyl ethanamine) is reacted with VC solution in toluene in presence of anhydrous potassium carbonate. The crude product is isolated by removal of the solvent.

Crude product (Itopride Base) is treated with carbon in hot acetone. After removal of carbon, addition of acetone HCl leads to formation of the Itopride HCl.

40. ETIRACETAM

AB-6 (methyl 2-bromobutanoate) is reacted with ammonia in autoclave and methanol as solvent. The produced 2-Aminobutanamide is reacted with 4-CBC (4-Chlorobutanoyl chloride) in presence of KOH, sodium sulphate and catalyst in MDC. Ethyl acetate is added followed by reflux. Solid is further filtered to get Etiracetam.

41. EFLETIRIZINE

Difluorobenzhydryl chloride is reacted with hydroxyl ethyl piperazine in presence of potassium iodide and also in presence of sodium carbonate to form Bis -4-fluorobenzhydryl piperazine ethanol, which was further reacted with sodium methoxide and bromo acetic acid to obtain the product Efletirizine.

42. CARVEDILOL

4-Hydroxy carbazole is reacted with epichlorohydrin in the presence of sodium hydroxide in water-Dimethyl Sulfoxide mixture to get crude 4-(2,3- Epoxypropoxy) Carbazole(CAR-I) which further purified in isopropanol to get desired quality of CAR-I.

The CAR-I is reacted with 2-(2-methoxyphenoxy) ethylamine in the presence of glyme as solvent at higher temperature to get crude carvedilol. The crude carvedilol is purified by crystallization with ethyl acetate to give pure Carvedilol.

43. RASAGILINE MESYLATE

A mixture of 1-Amino indane (AI), propargyl chloride and potassium carbonate in acetonitrile are stirred under reflux and it afforded N-propargyl 1-amino indane. Unreacted AI is recovered by preparing oxalate salt. Then ML is treated with L(+) tartaric acid to yield PRSG-R tartarate salt.

PRSG-R tartarate salt is splitted using NaOH and product is extracted in MDC. MDC evaporated to obtain PRSG-R free base.

In a mixture of PRSG-R free base and IPA methane sulfonic acid is charged and stirred the reaction mixture is stirred at reflux temperature. The precipitated crystals are filtered to afford Rasagiline mesylate.

44. PRAMIPEXOLE DIHYDROCHLORIDE

Racemic 2,6-Diamino-4,5,6,7-tetrahydro-1,3-benzthiazole is first converted to the S-isomer using L(+) Tartaric acid which is condensed with propyl chloride & HCl to give Pramipexole Dihydrochloride.

45. FLUPIRTINE BASE

Flupirtine Maleate is suspended in a mixture of methanol. Liq ammonia is used to adjust pH and solids generated is filtered out. This wet cake is repulping in water.

46. TRIMETHOBENZAMIDE HYDROCHLORIDE

3, 4, 5 Trimethoxy benzoic acid (TMBA) is suspended in toluene and then reacted with Thionyl chloride. The acid chloride thus produced is added to a solution of ITO in toluene under controlled conditions. The resulting mixture is heated in toluene and then partitioned with alkaline water. Crystallization TMB base followed by reaction with MeOH- IPA – HCl mixture provides the product that is dried.

47. FASUDIL HYDROCHLORIDE

Synthesis of Fasudil hydrochloride which involves reaction of Isoquinolin-5-sulfonic acid is heated with thionyl chloride furnishing Isoquinolin-5-sulfonyl chloride HCl.

The reaction of Isoquinolin-5-sulfonyl chloride HCLwith homopiperazine in MDC yielding hexahydro-1-(5-isoquinolinsulfonyl)-1H-1, 4-diazepine i.e. Fasudil free base.

Finally the reaction of Fasudil free base with HCl in isopropyl alcohol and methanol gives hexahydro-1-(5-isoquinolinesulfonyl)-1H-1, 4-diazepine hydrochloride (Fasudil HCl).

48. **RAMOSETRON HYDROCHLORIDE**

Ramosetron hydrochloride is prepared by resolution of (1-methyl-1H-indol-3-yl) (4,5,6,7-tetrahydro-1H-benzimidazol-5-yl)methanone (Intermediate-1) with dibenzoyl tartaric acid yielded R-isomer. (R)-isomer is treated with aq. HCl in IPA formed Ramosetron hydrochloride.

49. LURASIDONE HYDROCHLORIDE

Lurasidone HCl is prepared from (1R,2S,3R,4S)-N-[(1R,2R)-2-[4-(1,2-Benzisothiazole-3yl)-1-piperizinylmethyl]-1-cyclohexylmethyl]-2,3-bicyclo[2,2,1]heptanedicarboxyimide (Lurasidone free base) reacted with aq. HCl in acetone yielded Lurasidone hydrochloride.

50. CICLETANINE HYDROCHLORIDE

4-chlorophenyl-5-[(3,4-isopropylidine)-2-methylpyridine]-methanol hydrochloride (Intermediate-3) is hydrolyzed followed by cyclization with aqueous concentrated hydrochloric acid to give 3-(4-Chlorophenyl)-1,3-dihydro-6-methylfuro[3,4-c] pyridine-7-ol hydrochloride (Cicletanine hydrochloride crude) .

Cicletanine hydrochloride crude is purified in methanol : IPA to give pure Cicletanine hydrochloride.

51. CELECOXIB

Cele-1 is prepared from 4-Methyl acetophenone and ethyltrifluoroacetate in toluene using sodium methoxide as a base. To slurry of sodium methoxide in toluene 4- Methyl acetophenone is added slowly and stirred. Then ethyltrifluroacetate is added slowly. Reaction mass is heated and stirred to complete the reaction. After completion of reaction, reaction is cooled and quenched with water. pH is made acidic by adding conc. HCl and product is extracted in toluene. Toluene layer is concentrated to give oil, which is taken in isopropanol, and water is added to obtain Cele – 1 in solid form. Cele-1 is filtered washed with water and dried.

Cele-1 and 4-Hydrazino benzene sulfonamide HCl are taken in ethanol and refluxed. After completion of reaction, reaction mass is cooled and filtered to remove excess unreacted 4-Hydrazino benzene sulfonamide. Water is added to ethanol filtrate to precipitate the product. Product is filtered and dried to get Celecoxib Crude.

Celecoxib pure is obtained from Celecoxib crude by crystallization in toluene. Celecoxib crude is dissolved in toluene and charcolized with activated carbon. Then reaction mass is cooled and ethanol is added to it. Reaction mass is filtered through celite bed followed by filtration. Filtrate is heated to distill out ethanol. The reaction mass is cooled and stirred. Product is filtered and wet solid is again crystallized with toluene to give pure Celecoxib.

52. OMEPRAZOLE

2-Chloromethyl-3, 5-dimethyl-4-methoxy pyridine hydrochloride (chloro compound) is condensed with 2-mercapto-5-methoxy benzimidazole (mercapto compound) in the presence of sodium hydroxide as a base in aqueous methanol to get sulfide compound.

Sulfide compound is oxidized with hydrogen peroxide in the presence of ammonium molybdate tetrahydrate as catalyst to get omeprazole Crude. Omeprazole Crude is further purified by acid base treatment followed by crystallization in the mixture of methanol & DCM to get pure omeprazole as a light sensitive solid.

Omeprazole Crude is taken in DM Water and sodium hydroxide solution is added to get omeprazole sodium as a clear solution. This solution is wash with dichloromethane and filtered to remove the insoluble solids .To this filtrate, aqueous ammonium acetate solution is added drop wise to isolate Omeprazole.

53. CLOPIDOGREL BISULFATE

Bromination of 2-chlorophenyl acetic acid is carried out using N-Bromo Succinimide (NBS) in EDC as a solvent and Azobisisobutyronitrile (AIBN) as a catalyst to give a Clopi-1 (Bromo-(2-Chlorophenyl) Acetic Acid [Bromo Acid]).

Esterification of Clopi-I is done using sulfuric acid as catalyst in methanol as a solvent and as well as reagent to give Clopi-2(Methyl bromo-(2-chlorophenyl) acetate[Bromo Ester]).

Condensation of 4,5,6,7,- tetrahydrothieno [3,2-c]pyridine HCl and Clopi-2 is carried out using potassium carbonate a base in DMF solvent to form condensed product and which is isolated as a sulfate salt of Clopi-3 (Racemic Clopidogrel bisulfate salt).

Clopi-3 is made a salt free using aq ammonia, then resolving the compound with (1R)-(-)-10-Camphor Sulfonic acid in acetone at ambient condition to give Clopi-4.

Clopi-4 is made a salt free by using sodium carbonate solution in water, and then isolated as a sulfate salt using sulfuric acid in mixture of ethylacetate and cylohexane solvent to get Clopidogrel Bisulfate.

54. DESLORATADINE

The reaction of N-methyl loratadine with ethyl chloroformate (ECF) gives loratadine (DESLO-I). During isolation of material, toluene layer is distilled out after salt filtration. Then, there is a carbon treatment in ethyl acetate followed by distillation of Ethyl acetate and finally DESLO-I (Loratadine) is isolated in Ethyl acetate and Cyclohexane.

Further reaction of loratadine in presence of caustic and DNS gives crude desloratadine, after completion reaction distilled out ethanol and give extraction with MIBK, isoaltion of material is in MIBK & Ethyl acetate.

Ccrude desloratadine is then purified in acetonitrile and ethyl acetate mixture to get Desloratadine.

55. SEVELAMER CARBONATE

Polymerization of Allyl amine is carried out in Con.HCl in presence of catalytic amount of amidino compound [2,2-Azobis- (-2-amidinopropane) dihydrochloride] to give SV-I (poly allylamineHCl).

SV-I is again polymerized to produce SV-II (Sevelamer Hydrochloride) in presence of caustic solution and using epichlorohydrine & sorbitan sesquiolate toluene as a catalyst.

Polymer of SV-II is reacted with sodium carbonate in presence of water at ambient temperature to give Sevelamer Carbonate.

56. CLINDAMYCIN PALMITATE HYDROCHLORIDE

Chlorination of Lincomycin hydrochloride monohydrate by using thionyl chloride as a reagent with DMF as a solvent, then protecting group of diol of CLINDA-I by using 2,2-Dimethoxy propane with PTSA catalyst in DMF solvent. CLINDA-II is isolate further in ethyl acetate. CLINDA-II further react with palmityl chloride and pyridine as a base in MDC solvent and isolate in acetone. CLINDA-III deprotecting by using

aq. HCl after complete distillation isolate Clindamycin palmitate Hydrochloride in MDC & then acetone, purified with methanol to get Clindamycin Palmitate HCl.

57. ARMODAFINIL

Benzhydrol is reacted with Thioglycolic acid in presence of p- toluene sulfonic acid in DCM to prepare AR-I.

AR-II (Racemic) is prepared by oxidizing AR-I by Hydrogen peroxide in presence of glacial acetic acid in THF.

AR-II (Racemic) is resolved by making diasteriomeric salt with chiral auxiliary S-(-)-α-methyl benzyl amine and recrystallizing from water to get required isomer.AR-III.

AR–IV is prepared by esterifying AR-III with methyl Iodide in presence of anhydrous potassium carbonate in acetone.

AR-V is prepared by reacting AR-4 with Ammonia in Methanol followed by isolation in MDC and DIPE.
AR -V is crystallized from denatured ethanol to get Armodafinil.

58. AZITHROMYCIN MONOHYDRATE

AZM-I is prepared by condensing erythromycin base with hydroxyl amine hydrochloride in the presence of Tri ethyl amine and methanol as a solvent. After completion of reaction the mass is cooled, DM water added in reaction mass and pH of RM is adjusted by caustic lye, solid is isolated by filtration.

To the solution of sodium bicarbonate, added Dichloromethane and then AZM-I, to this mixture of p-toluene sulphonyl chloride solution in Dichloromethane added. After completion of reaction, adjusted by using HCl, layer separated, then aqueous layer basifies with caustic lye. Product isolated by filtration as erythromycin Imino ether (AZM-II).

AZM-III is prepared by hydrogenation of AZM-II in presence of Pt-C, as a catalyst using methanol as solvent media. Perchloric acid is being used to maintain the pH of reaction mass. After completion of reaction catalyst is filtered and solvent is evaporated completely to get

semisolid mass. Water and acetone is added to dissolve the mass and pH of solution is adjusted with caustic lye. Solid is isolated by filtration.

AZM-IV is prepared by methylation of AZM-III with aqueous formaldehyde solution in presence of formic acid and acetone as solvent. After completion of reaction, adjust pH of chemical reaction with caustic lye. Separate the organic & aqueous layer. Add water in acetone layer. Azithromycin wet solid is obtained by filtration. Azithromycin (wet cake) is dissolved in DCM. DCM is washed with caustic followed by water. Distill out DCM, concentrated mass stripped with methanol and adding water. Azithromycin solid is isolated by filtration.

Azithromycin is dissolved in denatured ethanol and charcolised. Add ethanol solution of Azithromycin in water and heat the reaction mass. Azithromycin monohydrate is isolated by filtration.

59. LANSOPRAZOLE

2-Chloromethyl-3- methyl- 4-(2,2,2-trifluoroethoxy) pyridine hydrochloride is reacted with 2-mercapto imidazole in presence of sodium hydroxide in methanol at ambient temperature to give Lanso-I.

Lanso-I is oxidized by using sodium hypochlorite solution in presence of aqueous sodium hydroxide solution in ethyl acetate to give Lanso-II (crude Lansoprazole).

Lanso-II is purified with aqueous ethanol in presence of aqueous ammonia to obtain purified Lansoprazole.

Lanso-III is recrystallisation in acetone and diisopropyl ether mixture to get Lansoprazole.

60. DIACEREIN

Sodium dichromate dihydrate react with Sulphuric Acid and get chromic acid.

Aloe emodine is oxidized using chromic acid and tetrahydrofuran as a solvent to give DCN-I.

DCN-I is reacted with propanoic anhydride in presence of sulfuric acid to get DCN-II.

DCN-II is purified in THF then hydrolyzed using sodium hydroxide in water to give DCN-IV.

DCN-IV is reacted with acetic anhydride in presence of sulfuric acid to get Diacerein crude and which is first purified with N-Methyl pyrrolidone & methanol mixture and then with N-Methyl pyrrolidone & water mixture.

61. MEMANTINE HYDROCHLORIDE

Bromination of 1,3-Dimethyladamantane gives bromo MMT.

Bromo MMT is reacted with acetonitrile & sulphuric acid and Acetamido MMT is formed.

Acetamido MMT is hydrolysed in presence of caustic gives memantine freebase.

Memantine hydrochloride is then prepared in THF solvent by using Aq.HCl and memantine free base.

62. ESZOPICLONE

Preparation of ESZ-I involves condensation reaction between pyrazine compound and chloro piperazine compound by using 1,8-diazabicyclo[5.4.0]undec-8-ene (DBU) as a reagent with MDC as a solvent.

ESZ-I is then purified in acetonitrile with carbon treatment to produce Racemic ESZ-II.

Enantiomeric seperation of ESZ-II by using Dibezoyl-D-tartaric acid (DBTA) in methanol solvent to ESZ-III. DBTA salt of ESZ-III break with sodium hydroxide to produce ESZ-IV.

The ESZ-IV is further purified in acetonitrile to produce Eszopiclone.

63. TOLTERODINE TARTRATE

Cyclization of P-Cresol with cinnamic acid and sulphuric acid formed TT-I.

Reduction of TT-I with sodium borohydride in IPA solvent is then to get TT-II.

TT-II is insitu stage in which Dimethyl Sulfate is used for methylation and further PTSCl (P-toluene sulphonyl chloride) react and gives TT-III.

Further reaction of TT-III with N,N-disopropyl amine gives amino compound. This amino compound is hydrolysed with HBr and water give TT-IV.

TT-IV is then broked by using ammonia to form Tolterodine base, then there is salt formation with L- tartaric acid gives Tolterodine tartrate.

64. DRONEDARONE HYDROCHLORIDE

2-Butyl-3-(4-hydroxybenzoyl)-5-nitro benzofuran treated with N-(3-chloropropyl) dibutylamine to form 2-n-butyl-3-[4-(3-di-n-butylamino-propoxy)benzoyl]-5-nitro benzofuran (INT-I).

Drone-I is hydrogenated and then treated with oxalic acid to form 5-amino 3-[4-(3-di-n-butylamino-propoxy) benzoyl]2-n-butyl benzofurandi oxalate (INT- II).

Drone- II is reacted with methane sulfonyl chloride to give Dronedarone hydrochloride.

Puritfication of Dronedarone (Crude) done in acetone to give pure Dronedarone hydrochloride.

65. FEXOFENADINE HYDROCHLORIDE

Esterification of 2-[4-(4-Chlorobutanoyl)phenyl]-2-methylpropanoic acid with Methanolic HCl to produce Methyl 2-[4-(4-Chlorobutyryl) phenyl-2-methylpropanoate (FEXO-1).

N-Alkylation reaction of Azacyclonol and FEXO-1 in presence of Potassium bicarbonate and Potassium iodide in Methyl-iso-butyl ketone (MIBK) & water under heating condition. After reaction completion separate organic and aqueous layer followed by distillation of Methyl-iso-butyl ketone, FEXO-2 isolated as solid material using denatured spirit and water.

KETO ESTER (FEXO-2) is treated with Sodium borohydride in Methanol & then hydrolysis using sodium hydroxide to obtain crude FEXO BASE (FEXO-3).

The crude FEXO BASE (FEXO-3) is purified twice, using methanol and acetone mixture to get pure FEXO BASE (FEXO-4).

FEXO-4 is treated with aqueous Hydrochloric acid in iso-propanol & then ethyl acetate added to isolate Crude FEXOFENADINE HYDROCHLORIDE (FEXO-5).

Fexofenadine hydrochloride (FEXO-5) is purified using a solvent mixture of methanol, iso-propanol and ethyl acetate to yield pure FEXOFENADINE HYDROCHLORIDE (FEXO-6).

66. TRAZODONE HYDROCHLORIDE

Reaction of [1,2,4]triazolo[4,3-a]pyridin-3(2H)-one(TZP) and1-(3-chlorophenyl)-4-(3-chloropropyl)piperazine.HCl (T2.HCl) to form Trazodone Crude :

Pottasium carbonate is added to a suspension of TZP in IPA. To the resulting suspension T2.HCl is added and the entire mass is reacted at reflux temperature. The resulted TZD Basereacted with excess HCl to give Trazodone.HCl crude.

Trazodone Crude to Trazodone HCl:

Trazodone.HCl crude is dissolved in Methanol at refluxing temparature. The reaction mass then allowed to cool. The solid product is removed by filtration and dried etc.

67. CONIVAPTAN HYDROCHLORIDE

Antranilic acid is treated with thionyl chloride in methanol. Refluxed, Methanol distilled to obtain AVCNP-1.

Methylanthrinilate(AVCNP-1) is treated with toluene-p-sulfonyl chloride in dry pyridine and the product crystallized from methanol

A mixture of AVCNP-2, 4-chlorobutane nitrile, anhydrous potassium carbonate, and potassium iodide in acetone is refluxed. After cooling, the reaction mixture is poured into of ice water. The precipitated white crystals is filtered, wash with water.

To a solution of AVCNP-3 in dimethyl formamide with catalyst TBAB(tetrabutyl ammonium bromide), is added to a suspension of sodium methoxide in dimethylformamide with stirring under nitrogen stream and cooling in an ice bath. After the addition is complete, the reaction mixture is poured into diluted hydrochloric acid with stirring and the mixture is stirred under cooling in an ice bath. The precipitated pale gray crystals is filtered, wash with water.

AVCNP-4 is heated in a mixture of acetic acid and concentrated hydrochloric acid at reflux. The mixture is cooled, poured into water, and filtered to remove insoluble materials. To the filtrate, sodium hydroxide aqueous solution and ethyl acetate is added. The organic and aqueous layers are separated, and the organic layer is washed with water then concentrated to give an oily product (AVCNP-5).

AVCNP-5, triethyl amine and P-Nitrobenzoyl Chloride in dichloromethane is stirred. The mixture is washed with sodium bicarbonate aqueous solution and then concentrated. The resulting crystals are filtered off and dried to give slightly brown crystals and purified using methanol to get AVCNP -6.

Bromine is added to a solution of AVCNP-6 in dichloromethane. The mixture is washed with water and sodium bicarbonate aqueous solution then concentrated. The resulting crystals is purified in methanol to get AVCNP-7.

Ethanmidedine Hydrochloride and potassium carbonate are added to a solution of AVCNP-7 in Dichloromethane , and the mixture is heated. The mixture is cooled , washed with water and then concentrated, the resulting crystals is filtered off and dried to obtain AVCNP-8

AVCNP-8 is hydrogenated over raney nickel at under hydrogen atmosphere in methanol. The catalyst is removed by filtration and wash with methanol. Water is poured into the filtrate, and the resulting crystals is filtered off and dried to get AVCNP-9.

To a solution of biphenyl-2-carboxylic acid in acetonitrile and pyridine ,charge AVCNP-9 .The mixture is warmed slowly . After completion of the reaction, a solution of hydrogen chloride in ethyl acetate is added to the mixture and stirred. The resulting crystals are filtered off and dried to get final product.

68. MIRABEGRON

ATTA ((2-amino-1,3-thiazol-4-yl)acetic acid) is added to clear solution of R-APPE.HCl ((1R)-2-{[2-(4-aminophenyl)ethyl]amino}-1-phenylethanol) in water and HCl. To the resulting slurry, DEC (N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride) is added. The reaction mass becomes clear. After completion of reaction, reaction mass is basified using liq. ammonia solution. The reaction mass is filtered. Slurry wash of DM water are given to the wet cake. Wet cake obtained after slurry wash, is taken in to IPA. Then crude product is isolated.

Charcoal treatment to MIRA crude is given in methanol. After filtration through celite, methanol is recovered. IPA is then added in to reaction mass. Reaction mass is filtered and washed with IPA to get pure Mirabegron.

69. EFAVIRENZ

PMB-amino alcohol is reacted with DDQ (4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile) in toluene as a solvent to give a cyclic aminal compound which is further hydrolyzed using sodium hydroxide and then reduced using Sodium borohydride to give crude amino alcohol (EFA-I).

Crude amino alcohol (EFA-I) is purified by dissolving it in Toluene & Methyl tert. butyl ether and then isolating it by using n-Heptane.

Pure amino alcohol (EFA-I Pure) is reacted with 1,1 carbonyl diimidazole (CDI)in Dichloromethane to give Efavirenz which is purified further to get Efavirenz pure.

70. TELMISARTAN

Bibenzimidazole & bromomethyl ester is condensed in presence of sodium methoxide in DMFto give Telmi-I (Methyl 4'-[[4-Methyl-6-(1-methyl-1H benzimidazol-2-yl)-2-propyl-1H-benzimidazole-1-yl] methyl] biphenyl-2-carboxylate).

Telmi-I is hydrolyzed using potassium hydroxide in methanol & water mixture to give Telmisartan.

71. PIOGLITAZONE HYDROCHLORIDE

5-Ethyl-2-(2-(4- Nitro phenoxy)ethyl)pyridine (EPNB) is hydrogenated in presence of palladium catalyst to produce PGL-I, which is further diazotized using sodium nitrite solution in water to get diazotized PGL-I. It is further reacted with hydrogen bromide and methyl acrylate in presence of copper oxide (I) to get PGL-II.

PGL-II is cyclized using thiourea and sodium acetate in methanol to give PGL-III (5-({4-[2-(5-ethylpyridin-2-yl) ethoxy]benzyl}-2-imino-1,3-thiazolidin-4-one).

PGL-III is reacted with hydrochloric acid in water to give PGL-IV ((5-({4-[2-(5-ethylpyridin-2-yl) ethoxy]benzyl}-1,3-thiazolidin-2,4-dione).

PGL-IV is purified in DMF and water mixture to get PGL-V (pure Pioglitazone).

PGL-V is isolated as a hydrochloride salt using concentrated Hydrochloride acid in ethanol water mixture as a solvent to get Pioglitazone hydrochloride.

72. EMTRICITABINE

L-Menthyl Glyoxalate hydrate is first dehydrated and then reacted with 1,4-dithiane-2, 5-diol in toluene to give Emtri-I (1R,2S,5R)-5-methyl-2-(propan-2-yl)cyclohexyl (5R)-5-hydroxy- 1,3-oxathiolane-2-carboxylate.

Emtri-I is reacted with thionyl chloride in Dichloromethane, DMF as a solvent and Methane sulfonic acid as a catalyst to give a chloro compound which is further reacted with silylated 5-fluoro cytosine to give Emtri-III, [((2R, 5S)-5-(4-amino-5-fluoro-2-oxo-2H-pyrimidin-1-yl)-[1,3] oxathiolane-2-carboxylic acid, 2S-isopropyl-5R-methyl –1R-cyclohexyl ester)].

Reduction of Emtri-III is carriedout using sodium borohydride in water and ethanol as a solvent to give Emtri-IV (4-amino-5-fluoro-1-(2R,5S)-2-hydroxymethyl-[1,3} oxathiolane-5-yl)-1H- pyrimidin-2-one) which is isolated as a salicylate salt.

Emtricitabine crude is obtained by breaking the salicylate salt of Emtri-IV using Triethyl amine and isolating crude Emtricitabine.

Crude Emtricitabine is purified with ethanol & Triethyl amine to get pure Emtricitabine.

73. MESALAMINE

The catalytic reduction of the potassium salt of 5-Nitrosalicylic acid using Raney Nickel and hydrogen in presence of methanol and water and finally acidification with hydrochloric acid gives Mesalamine Crude.

Mesalamine crude is dissolved in water using aqueous alkali and then treated with sodium dithionite, filtered and finally precipitated by using dilute hydrochloric acid to give Mesalamine.

74. ZIPRASIDONE HYDROCHLORIDE

PBT free base is prepared by breaking hydrochloride salt in water with sodium hydroxide. Extracted in MDC & isolated in cyclohexane.

Crude Ziprasidone is prepared by reaction of PBT free base with CEOI in Sulfolane (as a solvent) in basic condition with use of potassium carbonate .After complete reaction quinched with acetone water, slurry wash with acetone water to get crude Ziprasidone.

Crude Ziprasidone is purified by dissolving it in THF at reflux temperature. Clear reaction mass is charcolized, distilled & charge methanol, chilled and filtered to get Pure Ziprasidone.

Pure Ziprasidone is converted to Ziprasidone HCl in methanol as a solvent & methanolic HCl as the reagent.

75. BAZEDOXIFENE ACETATE

4-Hydroxy propiophenone reacted with benzyl chloride in presence of K2CO3 in methanol is refluxed. Reaction mixture is added water and ERBFD-1 is isolated as solid.

ERBFD-1 treated with bromine in ethyl acetate to produce 1-[4-(benzyloxy) phenyl]-2-bromopropan-1-one. (ERBFD-2)

ERBFD-2 treated with 4-benzyloxy aniline hydrochloride in presence of triethyl amine in DMF at high temperature to formed 5-benzyloxy-2- (4-benzyloxy-phenyl)-3-methyl-1H-indole (ERBFD-5). The product is isolated as solid from methanol & purified from acetone.

Hexamethylamine reacted with 2-chloro ethanol in toluene, Aq. NaOH is added and product (ERBFD-16) is extracted in toluene. 2-azepan-1-ylethanol (ERBFD-16) is isolated as liquid.

ERBFD-16 is treated with thionyl chloride in toluene. Reaction mixture is cooled and filtered the solid product as hydrochloride salt of 1-(2-chloroethyl) azepane - ERBFD-17.

4-Hydroxy benzaldehyde reacted with ERBFD-17 in presence of potassium carbonate in DMF. Water is added to reaction mixture and product is extracted in ethyl acetate. Solvent is removed by distillation and 4-(2-azepan-1-ylethoxy) benzaldehyde (ERBFD-18) is isolated as oil.

ERBFD-18 is treated with sodium borohydride in methanol at low temperature. Reaction mix is added water and product extracted in dichloro methane. Solvent is distilled out under vacuum and [4-(2-azepan-1-ylethoxy) phenyl] methanol (ERBFD-19) is isolated as oil.

ERBFD-19 treated with dry HCl in THF, thionyl chloride is added to the reaction mixture. The volatile is distilled out under vacuum. THF is added and hydrochloride salt of 1-{2-[4-(chloromethyl)phenoxy]ethyl}azepane (ERBFD-20) is isolated as solid

ERBFD-5 treated with sodium hydride in DMF under chilling condition. ERBFD-20 is added to the reaction mixture at chilling temperature. The product is isolated from methanol and purified from ethyl acetate.

ERBFD-9 is hydrogenated in presence of Pd/C. After completion of reaction catalyst is removed by filteration. Solvent is distilled out u/vacuum. Acetone and acetic acid is added and isolated Bazedoxifene acetate

76. RABEPRAZOLE SODIUM

Chloro compound (Rabe-1) reacts with 2-Mercaptobenzimidazole (MBI) under basic pH in water. After reaction, mass is filtered to get rabeprazole sulfide. (Sulfide Compound)

Sulfide compound reacts with sodium hypochlorite to make sulfoxide compound in presence of methanol and water mixture which is further replaced by ethyl acetate and finally the slurry is filtered in cyclohexane to form Sulfoxide compound

Sulfoxide compound in presence of caustic pallets and DCM converts to Rabeprazole sodium which is further purified using denatured ethanol and finally filtered in DIPE.

77. NAFTOPIDIL

To a stirred slurry of sodium carbonate in aq. methanol, charge 1-(2-methoxyphenyl) piperazine hydrochloride stir mass and then add 1-(1-Naphthyloxy)2,3-epoxypropane. Further heat the mass and after completion of the reaction, filter the solids, wash with solvent and then with water to give crude Naftopidil.

Naftopidil is suspended in ethyl acetate under stirring and the mass is heated to get clear solution. Carbon treatment is given at same temp and filtered rapidly through Celite. Heat to get the clear solution and cooled.

The filtered mass is wash with chilled ethyl acetate, unloaded and dried under vacuum.

78. TENOFOVIR DISOPROXIL FUMARATE

Adenine is reacted with R-Propylene carbonate in presence of catalytic amount of NaOH in DMF to get TNF-I [(2R)-1-(6-amino-9H-purin-9-yl)propan-2-ol]

TNF-I is reacted with diethyl tosyloxymethyl phosphonate in presence of magnesium tert.butoxide in the mixture of DMF & tertiary butanol to get TNF-II as an oil. This TNF-II is hydrolyzed with concentrated Hydrochloric acid to get TNF-III, ({[(2R)-1-(6-amino-9 H-purin-9-yl)propan-2-yl]oxy }methyl) phosphonic acid).

TNF-III is reacted with chloromethyl isopropyl carbonate in presence of triethyl amine, Tributylammonium bromide (TBAB) in N-methyl pyrrolidone (NMP) to get TNF-IV as oil. TNF-IV is dissolved in IPA and treated with fumaric acid in IPA to get pure Tenofovir Disoproxil Fumarate.

79. RITONAVIR

Crude BDH succinate salt is purified in isopropylalcohol to get pure BDH succinate salt.

Pure BDH succinate salt and Nitro thiazole intermediate are made salt free by using sodiumbicarbonate and it reacts in ethylacetate to give condensed product of Rito-1 and which is further hydrolyzed using aqeous hydrochloric acid to give Rito-2 ((2S,3S,5S)-5-Amino-2-(N-((5-thiazolyl)-methoxycarbony)amino)-1,6-diphenyl-3-hydroxyhexane bis hydrochloride), as a hydrochloride salt.

Rito-2 is made salt free using aq ammonia, and then it is condensed with L- Valine intermediate in presence of N,N'-dicyclohexyl carbodiimide and 1-hydroxy benzotriazole to give Ritonavir.

Annexure – 3

LIST OF HAZARDOUS CHEMICALS

S. No.	Name of Hazardous Chemical (as per MSIHC Rules)	Maximum quantity of Hazardous Chemical								
		Unit	Existing			Addn. Proposed			Total	
			QTY.	CAP.	TOL. VOL.	QTY.	CAP.	TOL. VOL	QTY.	TOL. VOL
1	Acetic Acid	MT	1	15	15	4	20	80	5	95
2	Hexane	KL	1	20	20	2	20	40	3	60
3	Methanol	KL	4	20	80	2 1	20 40	80	7	160
4	O-Xylene	KL	1	20	20	0	0	0	1	20
5	Toluene	KL	1	20	20	2	20	40	3	60
6	Chloroform	KL	1	10	10	2	20	40	3	50
7	IPA	KL	2	20	40	3	20	60	5	100
8	MDC	KL	1	20	20	4 1	20 30	110	6	130
9	Ethyl Acetate	KL	1	20	20	2	20	40	3	60
10	Acetone	KL	1	20	20	3	20	60	4	80
11	Sulphuric Acid	KL	1	15	15	0	0	0	1	15
12	HCl Acid	KL	0	0	0	2	15	30	2	30
13	Ammonia	Nos of Cylinders	252			0			252	
14	Hydrogen	Nos of Cylinders	75			0			75	
15	Epichlorohydrin	KL	0	0	0	2	20	40	2	40
16	Cyclohexane	KL	0	0	0	2	20	40	2	40
17	Dimethyl Formamide	KL	0	0	0	2	20	40	2	40
18	Pyridine	KL	0	0	0	2	20	40	2	40

Annexure – 4

LIST OF HAZARDOUS WASTE

S. No.	Hazardous Waste	Cat. No.	Existing (MTA)	Addn. Proposed (MTA)	Total (MTA)	Mode of disposal
1.	Used / Spent Oil	5.1	2.4	12.6	15	Collection, Storage, Transportation, Disposal by selling to registered Re-Refiners / Recyclers / disposal at CHWI
2.	Process Residues & Waste	28.1	900	14258	15158	Collection, Storage, Transportation, Disposal at common TSDF (Incineration/ land filling) / Co-Processing / Waste Mix Facility
3.	Spent Carbon	28.2	3	1052	1055	Collection, Storage, Transportation, Disposal at common TSDF (Incineration) / Co-Processing / Waste Mix Facility
4	Spent Catalyst	28.2	-	139	139	Collection, Storage, Transportation, Disposal at common TSDF (Incineration) / Off-site recovery at units from where catalyst is procured / other units doing recovery
5	Off Specification Products	28.3	-	-	What So Ever Generated	Collection, Storage, Transportation, Disposal by Incineration at CHWI/ / Co-Processing / Waste Mix Facility
7	Spent Organic Solvents	28.5	1082.64	-	What So Ever Generated	Collection, Storage, Transportation, Disposal at common TSDF (Incineration) / Off-site recovery/ Sale to authorized vendors / End Users / Co-Processing / Waste Mix Facility
8	Discarded Containers / Barrels / Linears contaminated with hazardous wastes / chemicals	33.3	7200 Nos./ yr	-	What So Ever Generated	Collection, Storage, Decontamination & Sale to authorized vendors / disposal at common TSDF

S. No.	Hazardous Waste	Cat. No.	Existing (MTA)	Addn. Proposed (MTA)	Total (MTA)	Mode of disposal
9	ETP Sludge	34.3	180	2520	2700	Collection, Storage, Transportation & disposal at common TSDF/ Co-processing / Waste Mix Facility
10	Ash from incineration of hazardous waste, flue gas residue	36.2	8.4	-8.4	0	Collection, Storage, Transportation & disposal at common TSDF
11	Spent Ion Exchange resin containing Toxic metals	34.2	-	0.5	0.5	Collection, Storage, Transportation & disposal at common TSDF (Incineration/ landfill)
12	Spent Acid	Sch.II-D2	126	1775	1901	Collection, Storage, Transportation & Sale to authorized vendors / end users
13	Liquor Ammonia	Sch.II-C1	480	13873	14353	Collection, Storage, Transportation & Sale to authorized vendors / end users
14	ATFD Solids	34.3	-	4327	4327	Collection, Storage, Transportation & disposal at common TSDF