3.2.S.2.2 Description of the Manufacturing Process and Process Controls

1. Outline of the Manufacturing Process of Irbesartan

1.1 Synthesis Route

The starting material for synthesis of Irbesartan are 2-butyl-1, 3-diazaspiro [4,4] non-1-en-one hydrochloride (BDS) and n-(triphenylmethyl)-5-(4'-bromomethyl biphenyl-2-yl-)tetrazole (BBTT). These two starting materials react in the presence of sodium hydroxide and tetrabutylammonium hydrogen sulfate in toluene and water to generate IRB01. The triphenylmethyl group of IRB01 is subsequently removed by treatment with hydrochloric acid to produce IRB02 which is Irbesartan in the form of its hydrochlorid salt. IRB02 is then treated with sodium hydroxide to obtain crude Irbesartan. It is subsequently crystallized in 95% ethanol, collected and dried to produce Irbesartan drug substance.

The synthetic process is illustrated in Fig. 3.2.S.2.2-1.

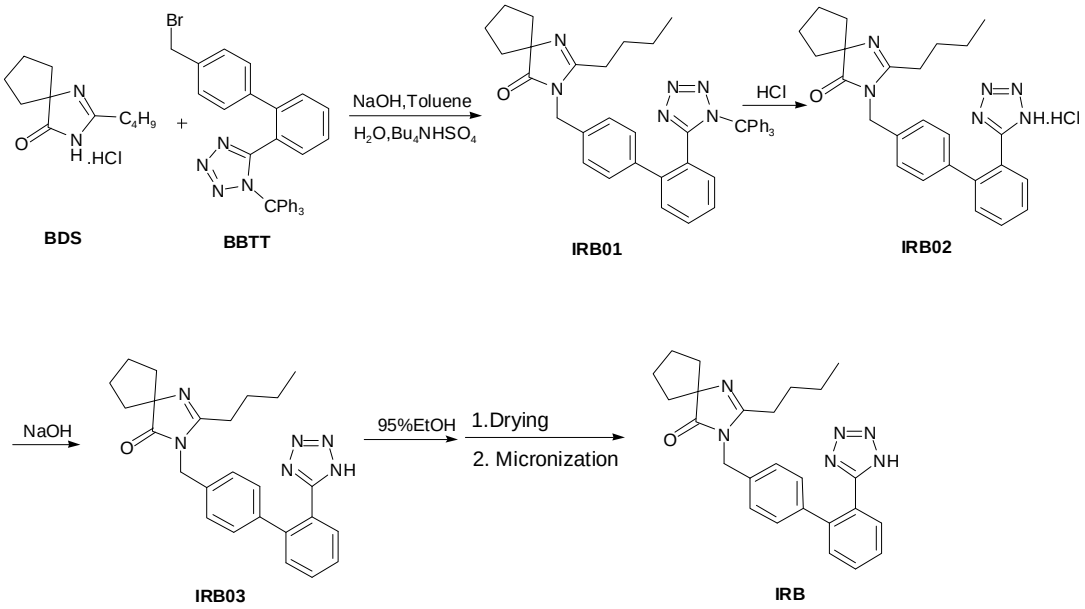

Fig. 3.2.S.2.2-1 Synthetic route of Irbesartan

1.2 Flow Chart of Irbesartan Manufacture

A flow chart of the manufacturing process is shown in Fig. 3.2.S.2.2-2 and the narrative description of the manufacturing process is presented in the following section.

Step I: Alkylation Reaction

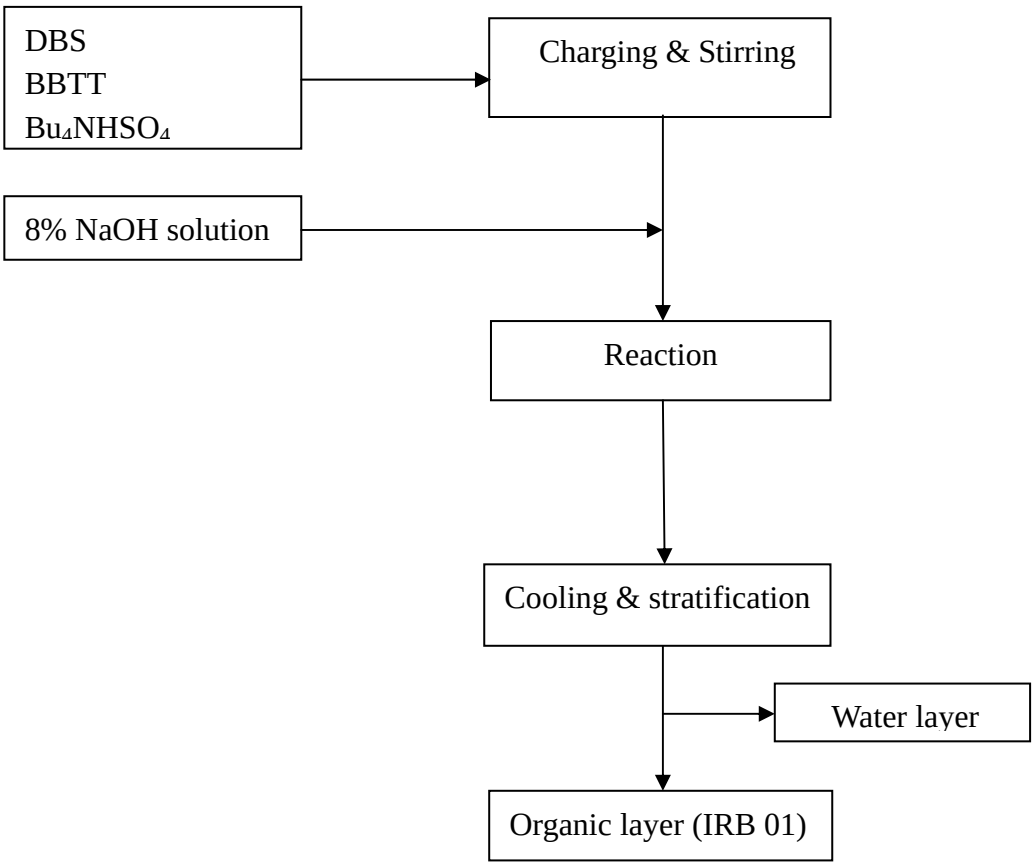

Fig. 3.2.S.2.2-2 Flow Chart of Manufacturing Process

Step II: Deprotection Reaction

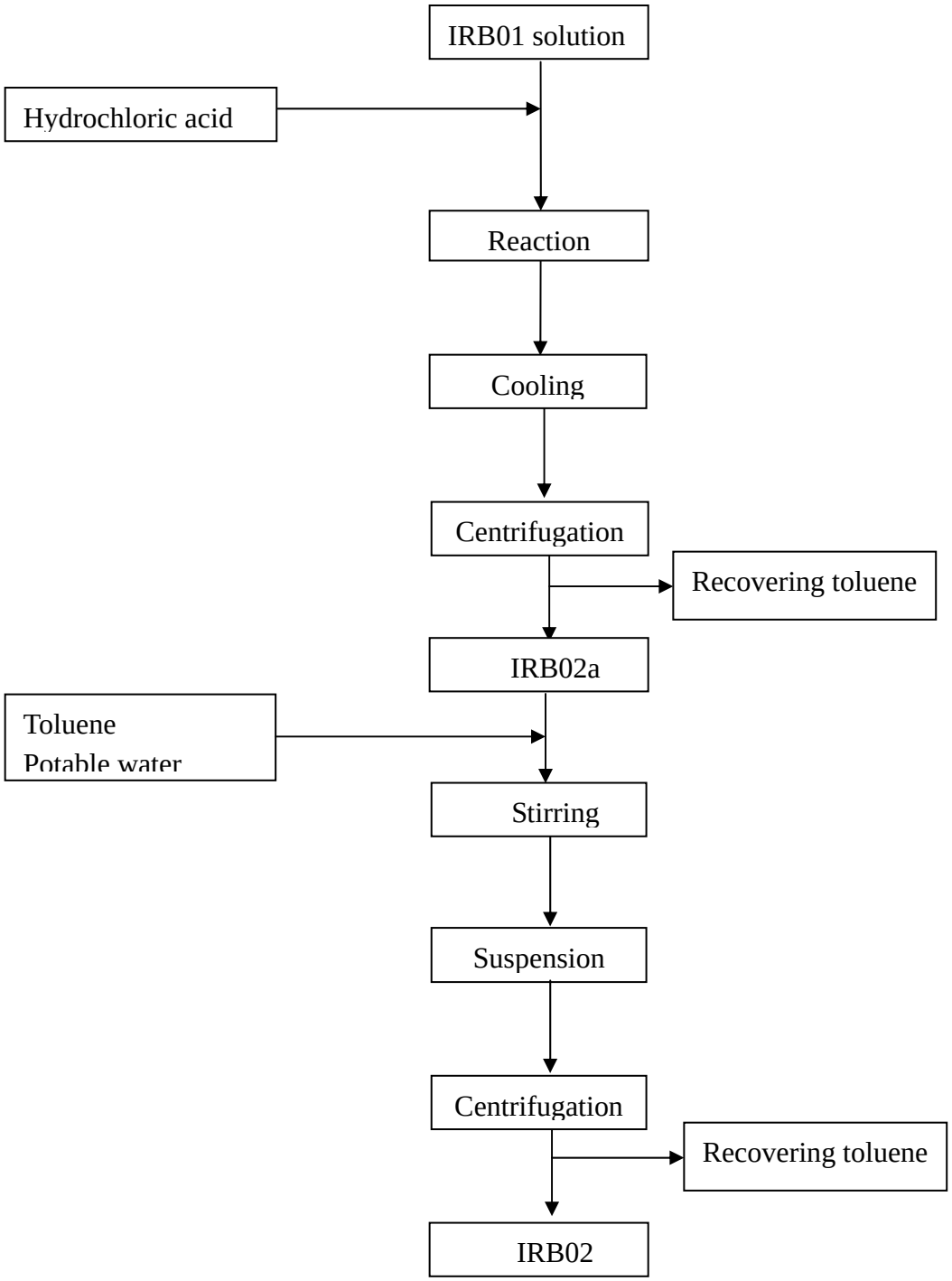

Fig. 3.2.S.2.2-2 Flow Chart of Manufacturing Process (continued)

Step III: Deprotonation Reaction

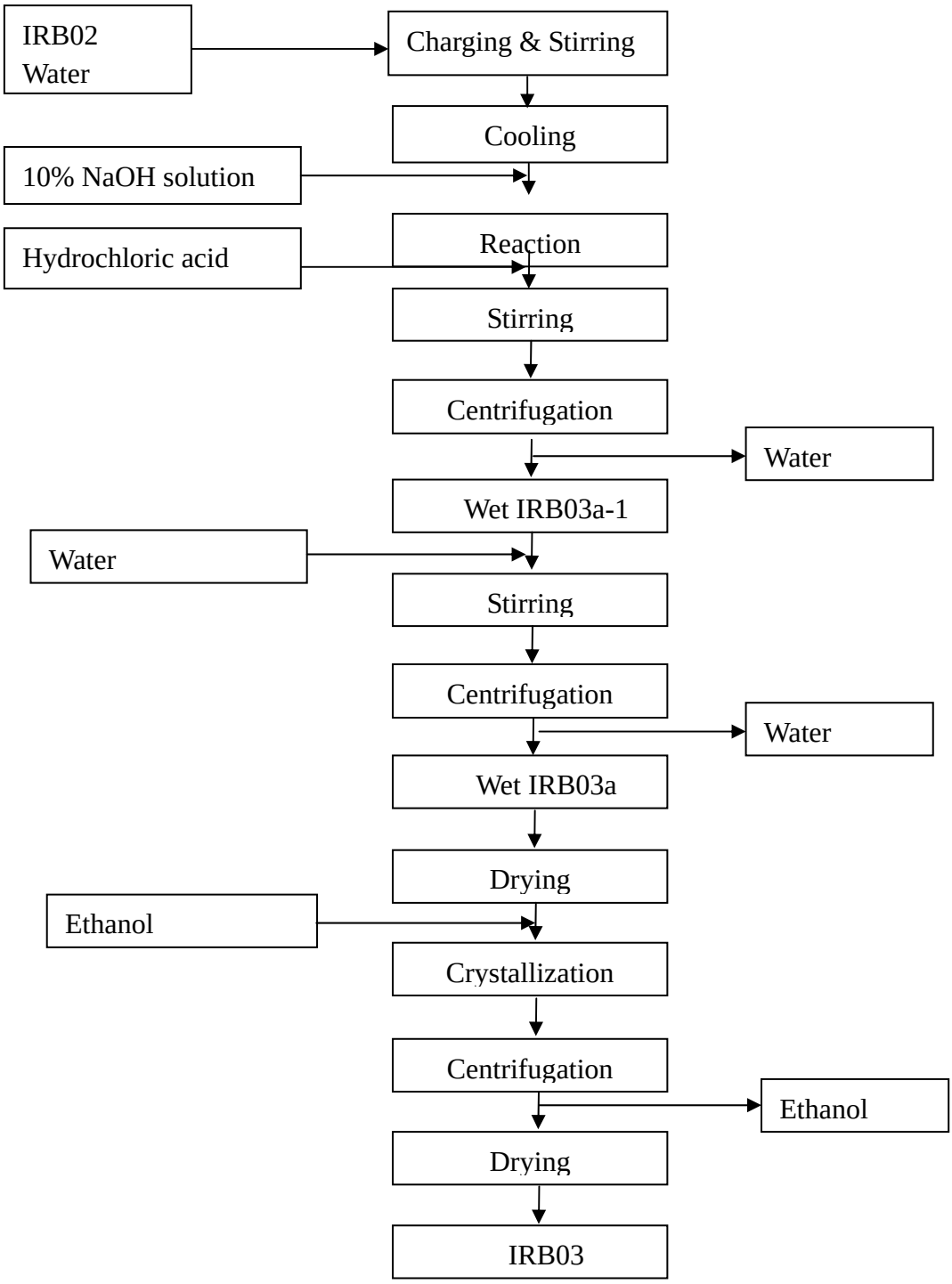

Fig. 3.2.S.2.2-2 Flow Chart of Manufacturing Process (continued)

Step IV-VI: Refining ~ Packaging and Labeling

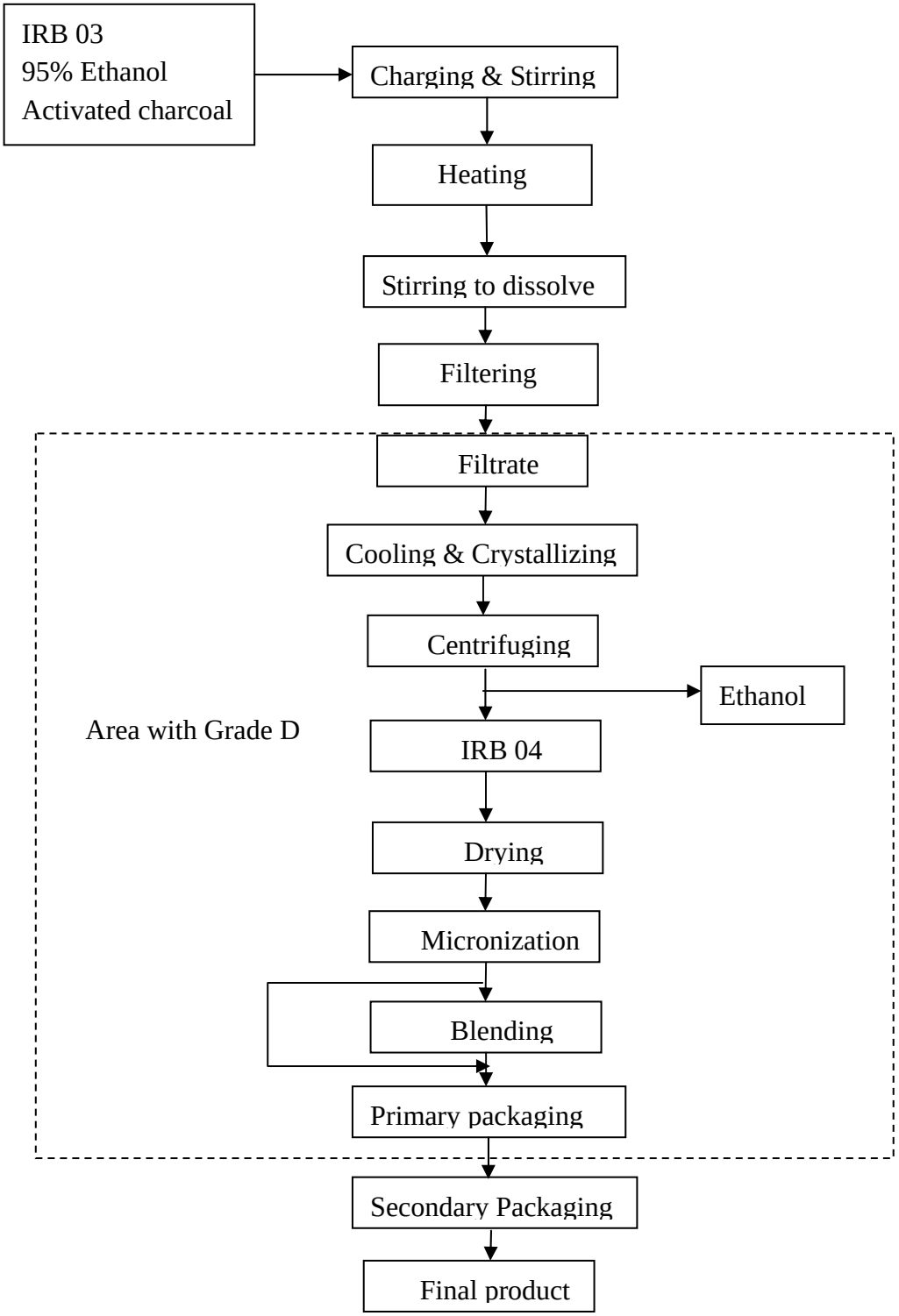

Fig. 3.2.S.2.2-2 Flow Chart of Manufacturing Process (continued)

2. Description of Manufacturing Process and Process Controls

2.1 Step I: Alkylation Reaction to Produce IRB01

The detailed schematic process for preparing IRB01 is provided in Fig. 3.2.S.2.2-3. And the chemicals used in this step are listed below:

Table 3.2.S.2.2-1 Materials for the Preparation of IRB01

Materials	Code	Grade	Weight Ratio	Reference Quantity (kg)
BDS	Y743	Industrial	1.0	60
BBTT	Y744	Industrial	2.0~2.1	123
Sodium hydroxide	Y030	Industrial	0.5~0.6	32
Tetrabutylammonium hydrogen sulfate	Y742	Industrial	0.07~0.08	4.5
Toluene	Y049	Industrial	17~18	1040
Potable water	EX-004	-	6.5~7.0	400

Procedure

To a 2000 L glass-lined reactor, 60 kg of DBS, 123 kg of BBTT, 4.5 kg of Tetrabutyl ammonium hydrogen sulfate and 1040 kg of toluene are introduced in sequence. The resulting mixture is stirred and the temperature is kept below 30 ^{o}C.

To the reaction system, 432 kg of 8% sodium hydroxide solution (32 kg of sodium hydroxide was dissolved in 400 kg of potable water) is added dropwise under 40 ^{o}C. Then the solution is heated gradually to 85 ± 2^{o}C.

The reaction is monitored with HPLC. When BBTT in the reaction mixture is detected at concentration of not more than 0.5%, the heating is stopped. The reaction mixture is cooled down to 30 ± 5^{o}C and allowed to stratify. The organic layer is collected and used in the next step directly.

2.2 Step II: Deprotection Reaction to Produce IRB02

The detailed process for preparing IRB02 is provided in Fig. Fig. 3.2.S.2.2-4 and the chemicals used are listed below:

Table 3.2.S.2.2-2 Materials for the Preparation of IRB02

Materials	Code	Grade	Weight Ratio*	Reference Quantity (kg)
IRB 01 solution from last step	IRB01	-	1 batch	1200
Hydrochloric acid	Y025	Industrial	4.2~5.0	270
Potable water	EX-400	-	10.5~12.5	690
Toluene	Y049	Industrial	4.5~5.5	300
* ratio is based on the amount of BDS used in the first step				

Procedure

IRB01 solution from last step is stirred in a 2000 L glass-lined reactor, and 510 kg of 4 mol/L hydrochloric acid solution (270 kg of hydrochloric acid is diluted with 340 kg of water) is added dropwise while the temperature is controlled at 25 ± 2^{o}C. The reaction mixture is heated gradually first to 35 ± 2^{o}C, then to 50 ± 2^{o}C, and finally to 65 ± 2^{o}C. The completion of the reaction is determining using TLC. The reaction is stopped when not more than 0.02% un-reacted IRB01 is detected.

The reaction mixture is cooled to 25 ± 5^{o}C and centrifuged. After centrifuging, filter cake is collected and labeled as IRB02a. IRB02a is stirred with 300 kg of toluene and 350 kg of water at 25 ± 5^{o}C for 1 h and centrifuged. The filter cake is collected by filtration to obtain IRB02.

2.3 Step III: Deprotonation Reaction to Produce IRB03

The detailed process for preparing IRB03 is provided in Fig. 3.2.S.2.2-5 and the chemicals used are listed below:

Table3.2.S.2.2-3 Materials for the Preparation of IRB03

Materials	Code	Grade	Weight Ratio*	Reference Quantity (kg)
IRB02	IRB 02	-	1 batch	132
Sodium hydroxide	Y030	Industrial	0.40~0.50	27
Hydrochloric acid	Y025	Industrial	0.8~1.2	60
Potable water	EX-004	-	29~35	1865
Anhydrous ethanol	Y050	Industrial	5.0~10.0	550
* ratio is based on the amount of BDS used in the first step				

Procedure

To a 2000 L glass-lined reactor, 300 kg of potable water and 1 batch of IRB02 are added at room temperature. The mixture is stirred and cooled to 5 ± 2°C, and 297 kg of sodium hydroxide solution (27 kg of sodium hydroxide is dissolved in 270 kg of water) is added dropwise under 10°C.

The resulting solution is stirred at 5 ± 2°C for about 1 h until the solution is clear. To the solution, 518 kg of diluted hydrochloric acid (60 kg of hydrochloric acid is diluted with 458 kg of water) is added dropwise within 3~4 h until the pH of the solution is 2.7~3.2. White precipitate is observed and the resulting suspension is stirred for 20 min. pH of the solution is tested again to be 2.7~3.2 and the suspension is stirred for 1 h before it is centrifuged and filtrated. The filter cake is labeled as IRB3a-1.

IRB3a-1 is stirred in 664 kg of water at 25 ± 5°C and followed by centrifugation, filtration and drying at 60 ± 5 °C until water content is less than 10.0% to provide IRB03a.

IRB03a is stirred in 550 kg of anhydrous ethanol at 78 ± 3 °C until the solution becomes clear. The mixture is then cooled gradually first to 40 ± 5 °C and then to 0 ± 5°C. The mixture is centrifuged and filtrated. The filter cake is dried at 60 ± 5°C. Samples are checked until the water content is less than 6.0% to provide IRB03.

Yield calculation

The yield of the first three steps is calculated using the formula below. The expected yield range is 70.0 ~ 99.0%.

$$Y = \frac{W_{IRB03}}{W_{BDS}} \times 100\%$$

In which,
W_{IRB03} - Weight of IRB03, kg;
W_{BDS} - Weight of BDS used in the first step, kg;

2.4 Step IV: Purification to Produce IRB04

The process for preparing Irbesartan is provided in Fig.3.2.S.2.2-6 and the chemicals used are listed below:

Table 3.2.S.2.2-4 Materials for the Preparation of Irbesartan

Materials	Code	Grade	Weight Ratio	Reference Quantity (kg)
IRB 03	IRB03	-	1.0	86
Ethanol	Y050	Industrial	7.0~14.0	830
Activated charcoal	Y064	Pharmaceutical	0.005~0.006	0.5

Procedure

To a 2000L decolorizing reactor, 1 batch of IRB03, 550 kg of ethanol and 0.3 kg of active charcoal are added in order. The resulting mixture is heated to 78 ± 3 ^{o}C and stirred. After the solution becomes clear, it is filtered and the filter cake is rinsed with ethanol which is preheated to 78 ± 3 ^{o}C.

The filtrate and the eluate are transferred to a 2000 L stainless steel crystallizing reactor. The resulting mixture is cooled gradually first to 40 ± 5 ^{o}C, and then to 0 ± 5 ^{o}C. After crystallizing, the crystals are collected by centrifugation and washed by ethanol which is cooled beforehand to provide wet Irbesartan with code of IRB04.

2.5 Step V: Drying and Micronization to Produce IRB05

Procedure

Drying: The wet IRB04 is transferred to a SZG-1000 double-cone drying oven at 60 ± 5 ^{o}C under a vacuum of not less than 0.085MPa. After drying for 24 h, samples are taken and tested. When the water content is determined as less than 0.5% and residual ethanol as less than 5000ppm, it is cooled to below 35^{o}C, and transferrd into PE bags.

Micronization: The dried Irbesartan is grinded in a FZB-150 micronization and granulating machine which is equipped with an appropriate size sieve. The Irbesartan is collected in PE bags. The product is weighed and marked as IRB05.

Yield calculation

The yield of the purification, drying and micronization is calculated using the formula below. The expected yield range is 70.0 ~ 100.0%.

$$Y = \frac{W_{IRB05/IRB} + W_{sample}}{W_{IRB03}} \times 100\%$$

In which,
$W_{IRB05/IRB}$ - Weight of IRB05/IRB, kg;
W_{IRB03} - Weight of IRB03, kg;
W_{sample} - Weigh of the sample taken, kg;

2.6 Step VI: Blending, Labeling and Packaging

Procedure

If necessary, several batches of the qualified IRB05 are blended in a SZG-2000 stainless steel double-cone blender and blended with speed of 8 rpm for 20±1 min to form a single batch. The maximum quantity of material charged to the blender should not be more than 150 kg.

Final product is collected in double PE bags and weighed. Both bags are closed tightly and transferred to a packing room where they are placed in a kraft paper drum.

Material Balance Calculation

The material balance of the micronization or blending stage is calculated using the formula below. The expected material balance range is 98.0 ~ 100.0%.

$$B = \frac{W_{packaged} + W_{remain} + W_{sample}}{W_{irb}} \times 100\%$$

In which,
$W_{packaged}$ - Weight of Irbesartan after packaged, kg;
W_{remain} - Weight of Irbesartan remainder after packaging, kg;
W_{sample} - Weight of the sample, kg.
W_{irb} - Weight of the dried Irbesartan before micronization or blending, kg;

3. Batch Numbering System

The product blended in a single blender forms a commercial batch. Therefore the maximum batch size is 150 kg.

The batch number of finished product is expressed as IRB-XXYYZZZ, in which IRB is the code for Irbesartan, XX represents the last two digits of the year, YY is the month and ZZZ is the serial number in the month. All batches produced in any particular month are numbered consecutively. For example, IRB-12080001 is the first batch of Irbesartan manufactured in August, 2012.

4. Reprocessing and Reworking

Reprocessing is performed according to the ICH Harmonized Tripartite Guideline, *Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients*.

Any batch of the product or intermediate that fails to meet the specification during manufacture may be reprocessed by repeating the procedures described in the appropriate section of the manufacturing process and process control of this dossier.

Each non-conforming batch will be reviewed to determine its suitability for reprocessing. All reprocessing will be reviewed and approved by the Quality Assurance Unit.

There are currently no reworking procedures in place for this product.

5. Recovery of Solvents and Reagents

The solvent listed in the table below is used in the manufacturing process and can be recovered and reused. The recovered solvents and reagents should meet the requirements of the specifications described in *Section 3.2.S.2.3.3* of this dossier.

Table 3.2.S.2.2-5 Summary of Recovery Reagents and Solvents

Name	Code	Source	Recovery Procedure	Use of the Solvent
Toluene	RY049	1. Reaction solvent in Step I 2. purification solvent in step II	Step 1: Stratification and separation with water layer. Step 2: adjusting pH to be 6-8. Step 3: distillation	Used in the same process

3.2.S.2.2 Manufacturing Process and Process Controls (Drug Product Manufacturer)

Complete information regarding the manufacturing process and process control of Irbesartan drug substance is provided in the API manufacturer's submission data (*3.2.S.2* Irbesartan) in this dossier.

Irbesartan drug substance is manufactured by Changjiang Pharm. The drug substance is delivered to Sunshine Lake Pharma (hereinafter called SLP) with a certificate of analysis (COA) issued by the API manufacturer.

Irbesartan drug substance will be tested for release by SLP to ensure the compliance with the in-house specification established based on the current Ph.Eur. general chapter (the analytical procedures are provided in section *3.2.S.4.2*). The drug substance would be performed for a micronization processing step if the particle size distribution cannot meet the in-housed requirement (D_{90}<15μm) in section *3.2.S.4.1* in this dossier.

The micronization process involves the following steps:

a. Install a stainless steel 120-mesh screen on the Universal Pulverizer. Set the rotor speed at 93%.

b. Charge the pulverizer with the drug substance and micronize until the particle size meets the acceptance criteria of D_{90}<15μm.

c. After the micronization is complete, calculate the reconciliation and yield as follows:

Reconciliation: $(A_2+A_3+A_5)/A_6\times100\%$
Yield: A_2/A_6
$A_6= A_1- A_4$

Wherein:
A_1: Total weight of drug substance received
A_2: Net weight of drug substance micronized
A_3: Weight of the test sample
A_4: Weight of the primary package bag
A_5: Weight of the rejected materials
A_6: Net weight of drug substance received

d. The micronized Irbesartan drug substance is packaged into double layer low density polyethylene (LDPE) bags. The bags are sealed and labeled, ready for sampling and releasing tests.