3.2.S.2.6 Manufacturing Process Development

The overall purpose of the process development is to investigate and optimize manufacturing process of Irbesartan drug substance, which could produce consistently the finished product complying with the current Ph. Eur. monograph for Irbesartan. The manufacturing process of Irbesartan referred to the patent US20050176794A1[1] involves three steps below:

- Step I: Alkylation Reaction
- Step II: Deprotection Reaction
- Step III: Purification

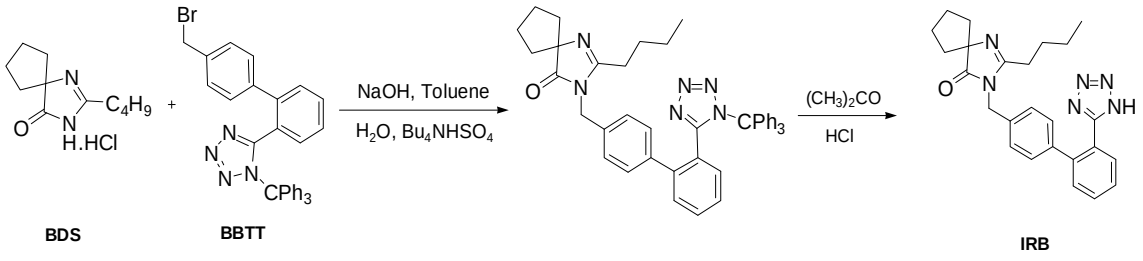
The manufacturing process of Irbesartan was first investigated and optimized at HEC Pharm R&D Center. The manufacture process developed includes four steps below:

- Step I: Alkylation Reaction
- Step II: Deprotection Reaction
- Step III: Deprotonation Reaction
- Step IV: Purification

The manufacture process was conformed in the kilo lab, then scaled up to the pilot plant at manufacturing facilities (Changjiang Pharm). The development work identified the critical process parameters (CPP) that must be controlled to ensure the desired product quality as well as ranges of these parameters. Finally three consecutive submission batches were produced at pilot scale under GMP conditions to the process is capable to consistently procedure the product in compliant with pre-determined quality requirements.

3.2.S.2.6.1 Process Development in Laboratory & Kilo Lab

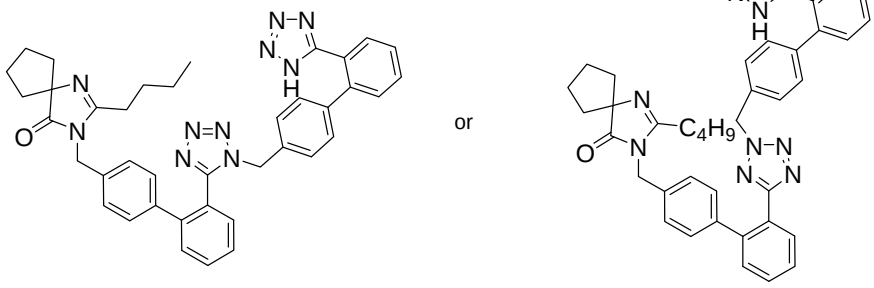
After literature investigation, we selected the following route as prototype route to reproduce and investigate the manufacturing process of Irbesartan:



1. Investigation of the Process at Laboratory

Irbesartan can be synthesized successfully through the above route, however, one unknown impurity exceeding 0.10% was out of the pre-determined specification of Irbesartan drug substance. The structure of impurity is identified by LC-MS as showed bellowed and is named as Impurity 2 (see *3.2.S.3.2 Impurities*).

Impurity 2:



In order to decrease impurity 2, we investigate the purification solvent, the addition way of BDS, and the reaction temperature basing on our prior experience and knowledge. The results are showed in the following table.

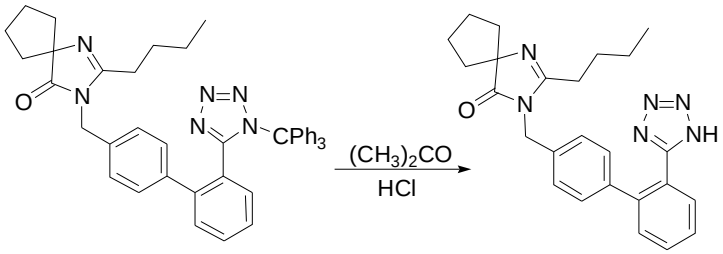
Table 3.2.S.2.6-1 Investigation of Decreasing the Impurity 2

Sample Code		Imp. 2	Purity of Irbesartan	Yield
1. Investigation of Purification Solvents				
Crude Irbesartan	IRB-02-HMN-0412	0.37%	93.04%	81.3%
Purified in Ethanol	IRB-03-HMN-0413-5B	0.35%	99.17%	73.6%
Purified in Acetone	IRB-03-HMN-0414-$(CH_3)_2CO$	0.15%	98.03%	93.7%
Purified in Toluene	IRB-03-HMN-0414-Toluene	0.30%	92.55%	94.2%
Purified in MTBE	IRB-03-HMN-0414-MTBE	0.48%	98.67%	92.6%
Purified in *n*-heptane	IRB-03-HMN-0414-C_7H_{16}	0.51%	98.14%	91.8%
2. Investigation of Addition way of BDS				
In one pot	IRB-03-HMN-0413-5B	0.35%	99.17%	73.6%
Dropwise	IRB-03-XY-0413-01JP	0.77%	98.67%	42.6%
3. Investigation of Reaction Temperature				
85°C	IRB-03-HMN-0413-5B	0.35%	99.17%	73.6%
75°C	IRB-03-XY-0414-01JP	0.21%	98.67%	42.6%
Acceptance Criteria		≤ 0.10%	–	–

The results show changing the purification solvent, the addition way of BDS, and reducing the reaction temperature cannot effectively reduce impurity 2 to be not more than 0.10%. Other measure must be taken to effectively reduce impurity 2.

After analysis, impurity 2 is generated from deprotected IRB01 reacting with BBTT. Detailed information of the formation of impurity 2 can refer to *3.2.S.3.2 Impurities*. It is considered to increase the amount of hydrochloric acid to make IRB01 deprotected and make the product generated in form of hydrochloride salt, which may prevent the formation of impurity 2. The prototype and improved chemical routes, and the impurities level in the product synthesized by the improved route are showed below:

Prototype route of Deprotection:



The improved route of Deprotection:

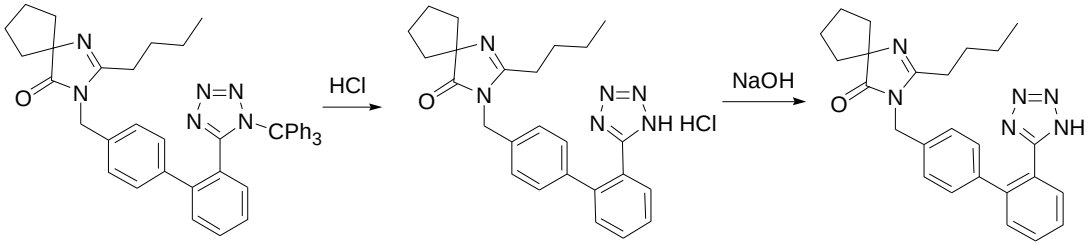
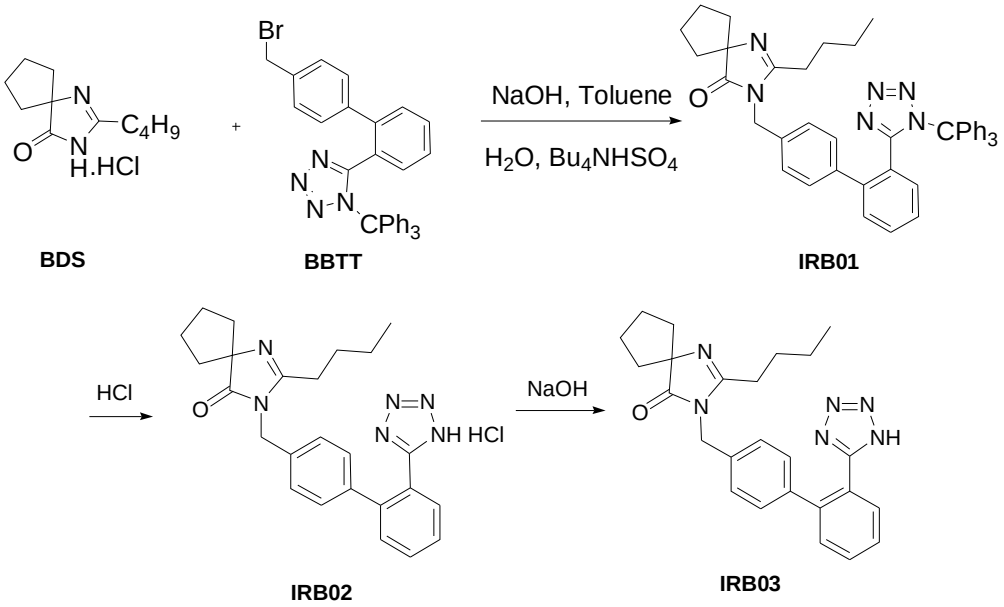


Table 3.2.S.2.6-2 Impact of Deprotection Method on the Content of Impurity 2

Quantity of BDS	Impurity 2	Purity of Irbesartan	Yield
6g	0.04%	99.73%	67.0%
12g	0.07%	99.62%	69.7%
60g	0.05%	99.67%	78.1%
Acceptance Criteria	≤ 0.10%	–	–

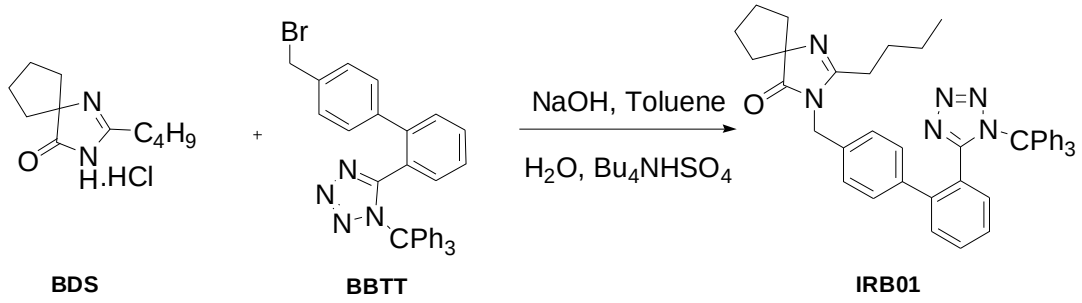
Conclusion

The results above demonstrate that the improved deprotection method can effectively reduce the formation of impurity 2. Thus, the synthesis route described below can be employed for the manufacture of Irbesartan to produce the qualified finished product.



2 Optimization of the process for each step at laboratory

Step I: Alkylation reaction



BDS reacts with BBTT in solvents of water and toluene in the presence of sodium hydroxide and tetrabutylammonium hydrogen sulfate (Bu_4NHSO_4) as phase transfer catalyst to provide IRB01.

Based on our experience, phase transfer catalysts can usually affect the reaction rate, and reaction temperature can affect the impurities, to investigate the best condition of this reaction, different phase transfer catalysts and different reaction temperature are studied.

(1). Investigation of phase transfer catalyst

IRB01 is synthesized in heterogeneous solvents system of water-toluene, the usage of phase transfer catalyst is very important. The information of synthesizing in presence of different phase transfer catalysts are showed in the following table.

Table 3.2.2.6-3 Impact of Phase transfer catalysts on Reaction Speed

Phase transfer catalysts	Reaction time (hour)	Reaction result
–	>6	Incomplete
5% Bu_4NHSO_4	1.5	Complete
10% Bu_4NHSO_4	> 1.5	Incomplete
10% Bu_4NBr	> 1.5	Incomplete
10% Bu_4NI	>1.5	Incomplete

From the results, obviously, 5% Bu_4NHSO_4 is the best choice for the synthesis of IRB01. It is selected for the manufacturing of IRB01.

(2). Investigation of the reaction temperature

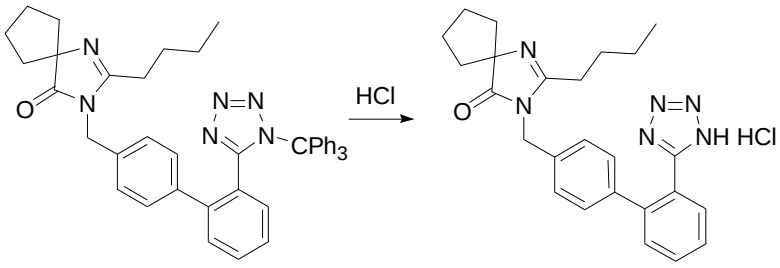
Based on our prior knowledge, reaction temperature can affect the reaction completion and the generation of impurities. Different reaction temperatures are investigated and the results are showed in the following table.

Table 3.2.S.2.6-4 Results with different reaction temperatures

Reaction temp.	Sample Code	Impurities (RT)			Reagents		IRB01
		10.25min	12.89min	19.01min	BDS	BBTT	
90°C	IRB-01-XY-0224-2.5	1.77%	2.47%	1.25%	0.21%	--	92.91%
85°C	IRB-01-XY-0304-02	1.78%	2.20%	0.97%	0.28%	--	93.65%
80°C	IRB-01-XY-0222-1	1.97%	2.61%	1.13%	0.24%	6.18%	86.60%
70°C	IRB-01-XY-0222-2	1.63%	2.21%	1.09%	0.27%	10.73 %	83.33%
60°C	IRB-01-XY-0224-60	1.37%	1.77%	1.31%	0.38%	21.73 %	73.09%

From the above results, low reaction temperature leads incomplete reaction, while high temperature makes increase of impurities, thus the reaction temperature is considered as a critical parameter, and a range of 85± 2°C is acceptable.

Step II: Deprotection reaction



IRB01 **IRB02**

IRB01 solution from last step is added with hydrochloric acid to make its protection group removed and provide IRB02.

Based on our experience, reaction temperature can affect the impurities, hydrochloric acid is the main reagent to deprotection in this step. To investigate the best condition of this reaction, different concentrations of hydrochloric acid and different heating temperature are studied.

As IRB01 is synthesized in water-toluene system, and is not isolated. IRB01 solution is directly used in the next step, and whether solvents of water and toluene are suitable for step II is investigated.

(1). Investigation of concentration of hydrochloric acid

Hydrochloric acid is used in this step to remove the protection group of triphenyl methyl from IRB01 and form IRB02 in form of hydrochloride salt. Different concentrations are investigated and the results are showed below.

Table 3.2.S.2.6-5 Reaction with different concentrations of hydrochloric acid

Con. of HCl	Impurities (RT)		IRB01	IRB02	Yield
	2.47 min	4.03 min			
2.5 mol/L	1.47%	0.91%	--	94.92%	86.7%
3.5 mol/L	1.15%	0.51%	0.49%	94.01%	87.3%

From the results, we can see the impurities and yield are not distinctly affected by the concentration of hydrochloric acid, so 2.5 mol/L of hydrochloric acid is selected in the manufacturing process for the consideration of reducing manufacturing cost.

(2). Selection of heating procedure

Based on our prior investigation, impurity 2-11 in IRB02 is the precursor of impurity 2 in final product which cannot be removed in the recrystallization. Detailed information can refer to *3.2.S.3.2Impurities*. And in the development, we found the heating procedure can affect the particle size of IRB02, which can further affect the elimination of impurity 2-11. So different heating procedures are investigated and the results are showed in the following table.

Table 3.2.S.2.6-6 Reaction with different heating procedures

Batch No.	Impurities (RT)						IRB02
	Unknown impurity (3.78min)	Unknown impurity (3.99min)	Impurity 2-9 (5.13min)	Impurity 2-4 (7.28min)	Impurity 2-3 (7.95min)	Impurity 2-11 (12.86min)	
IRB02-201110003	0.519%	0.579%	1.23%	0.036%	0.045%	0.095%	96.52%
IRB02-201111001	0.296%	1.099%	1.42%	0.040%	0.042%	0.055%	96.44%

For IRB02-201110003, the reaction mixture is directly heated to 65 ± 2°C, and for IRB02-20111001, the reaction mixture is gradually heated with a procedure of first to 35 ± 2°C (kept for 1 h), then to 50 ± 2°C (kept for 1 h), finally to 65 ± 2°C (kept for 1 h). The results show impurity 2-11 which is the precursor of impurity 2 can be reduced when the reaction mixture is heating gradually. So this heating procedure is employed for the manufacturing process of IRB02.

(3). Selection of solvents

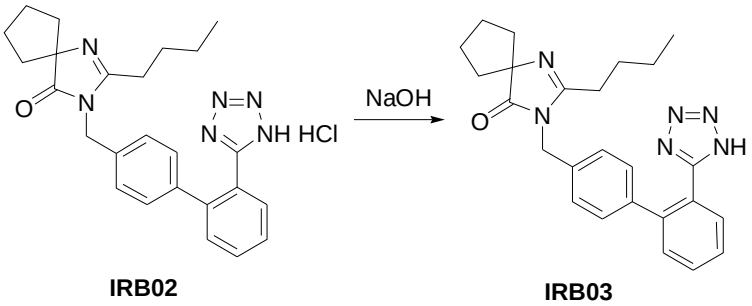
IRB01 is not isolated and used in this step directly in the solution. For the reaction solvents of synthesis of IRB01 are water and toluene, the suitability of these two solvents for synthesis IRB02 is investigated.

Table 3.2.S.2.6-7 Reaction with different solvents

Solvents	Impurities (RT)			IRB01	IRB02	Yield
	2.86 min	3.91min	10.75min			
Water-toluene	1.19%	1.49%	0.69%	--	95.40%	96.7%
Toluene	0.85%	0.99%	0.13%	--	97.77%	95.3%

From the results listed in the above table, it's obvious that IRB02 is generated in toluene with less impurity and more pure than it is in water-toluene system. So the reaction solution of IRB01 is not used in this step directly, instead, the organic layer including IRB01 was separated with the water layer, and then used in this step.

Step III: Deprotonation reaction



IRB02 **IRB03**

IRB02 reacts with sodium hydroxide to provide IRB03.

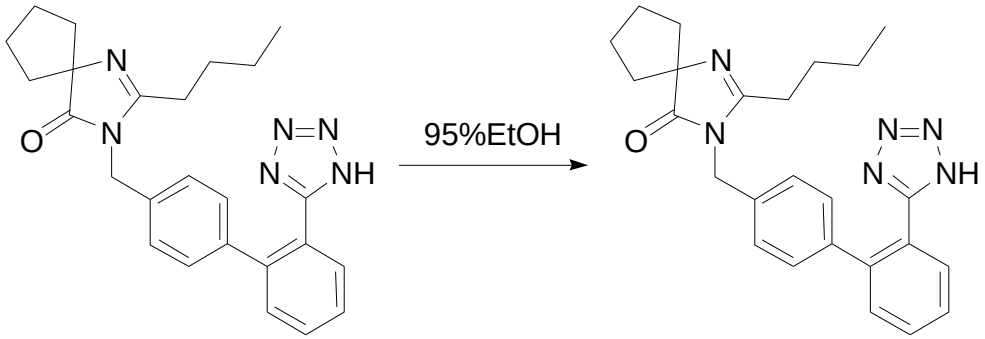
Theoretically, 1 equivalent of sodium hydroxide is needed to neutralize the hydrochloride salt of IRB02, and actually 1 equivalent is found not enough. In order to make sure IRB02 can be totally neutralized, more than 1 equivalent of sodium hydroxide is used. The excessive sodium hydroxide is then neutralized with hydrochloric acid. The amount of hydrochloric acid should be strictly controlled which is measured by pH of the reaction solution. The results of different pH are listed in the following table.

Table 3.2.S.2.6-8 Reaction with different pH

Sample Code	pH	Yield
HCS11044-42	1.5	72.4%
HCS11044-41	2.0	74%
HCS11230-35, 38	2.5	78.2%
HCS11230-34	2.75	80.37%
HCS11230-33,37	3.2	84.7%
HCS11230-33,40	3.3	79.6%
HCS11072-51~53	4.0	78.1%

The yield comes down when pH above 3.2 , as too less hydrochloric acid leads to incomplete precipitation of IRB03 from IRB03 sodium salt. However, the pH below 2.75 leads to the IRB03 hydrochloride could precipitate along with IRB03. Therefore, the pH value during the post-processing in this step is considered as a critical process parameter, and a pH range of 2.75-3.2 is acceptable. But considering the convenience of operation, it is proposed to be 2.7-3.2 in kilo lab based on our prior knowledge.

Step IV: Purification



According to US20050176794A1[1], Irbesartan can be crystallized in alcohols under 0-4 ºC, the process is confirmed in our lab, and the results are showed below.

Table 3.2.S.2.6-9 Test results after Crystallization

Sample Code	Solvent	Temp.	Max. Imp.	Purity of Irbesartan	Yield
IRB-03-HMN-0314-6eqKOH-jp	95% ethanol	0 ºC	0.12%	99.67%	68.8%
IRB-03-HMN-0315-7eqKOH-jp	95% ethanol	0 ºC	0.09%	99.60%	75.1%
Literature	Isopropanol	0-4 ºC	-	94%	84.3%

The product obtained with crystallization by 95% ethanol is very pure with acceptable yield, as ethanol is easy to be recovered in plant and cheaper than isopropanol. So 95% ethanol is used as crystallization solvent in manufacturing process of Irbesartan. In order to obtain consistent qualified product with desired crystal form and acceptable yield, the crystallization is considered as a critical process parameter, and for convenience of operation, it is proposed to be 0±5ºC based on our prior knowledge.

3. Reproducibility of the Process at Kilo lab

The kilo batches production was conducted at HEC Pharm R&D Center with reference to the manufacturing process of Irbesartan at small scale.

(1) Production and Results of Kilo Batches

The results of the three kilo batches of Irbesartan are summarized in table 3.2.S.2.6-11 to 12. All the tests meet the pre-determined specification.

Table 3.2.S.2.6-11 Production and Results of Three Kilo Batches

Step I: Alkylation reaction to produce IRB01						
Batch No.	**Reactant (BDS)**	**Reaction Temp.**	**Addition Temp.**	**Cooling temp.**	**IRB01 Solution (HPLC)**	
					Max. Imp.	**Purity**
IRB01-KG-A	0.6 kg	85 ºC	28 ºC	50 ºC	2.39%	91.07%
IRB01-KG-B	0.6 kg	85 ºC	27 ºC	50 ºC	2.39%	91.34%
IRB01-KG-C	0.6 kg	85 ºC	25 ºC	50 ºC	2.85%	91.42%
Expected Ranges		85±2 ºC	≤ 40 ºC	50±5 ºC	–	–

Step II: Deprotection reaction to produce IRB02						
Batch No.	**Batch size**	**Addition Temp.**	**Reaction Temp.**	**Yield**	**IRB02 (HPLC)**	
					Max. Imp.	**Purity**
IRB02.HCl-KG-A	1.17kg	47 ºC	64 ºC	77.2%	1.55%	95.66%
IRB02.HCl -KG-B	1.13kg	41 ºC	65 ºC	79.7%	1.79%	95.30%
IRB02.HCl -KG-C	1.07 kg	40 ºC	65 ºC	83.1%	1.93%	95.21%
Expected Range		≤ 50 ºC	65±5 ºC	–	–	–

Step III: Deprotonation reaction to produce IRB03						
Batch No.	**Batch size**	**Reaction Temp.**	**pH**	**Yield**	**IRB03 (HPLC)**	
					Max. Imp.	**Purity**
IRB02-KG-A	0.82kg	24 ºC	3	63.8%	6.90%	91.28%
IRB02-KG-B	0.75kg	6 ºC	3	71.8%	0.81%	97.75%
IRB02-KG-C	0.79kg	6 ºC	3	71.0%	0.68%	97.50%
Expected Range		room temperature	2.7-3.2	–	–	–

Step IV Purification & Step V Drying to produce final product				
Batch No.	**Batch size**	**Cooling temp.**	**Crystallization temp.**	**Drying temp.**
IRB03-KG-A	0.632kg	First: 79°C Then:40°C Finally:4°C	4°C	60°C
IRB03-KG-B	0.679kg	First: 78°C Then:40°C Finally:4°C	4°C	60°C
IRB03-KG-C	0.672kg	First: 79°C Then:40°C Finally:5°C	5°C	60°C
Expected Range		First: 78~80°C Then: 40± 5°C Finally: 0± 5°C	0± 5°C	60± 5°C

Table 3.2.S.2.6-12 Results of Irbesartan from Three Kilo Batches

Tests		Acceptance Criteria	Results		
			IRB03-KG-A	IRB03-KG-B	IRB03-KG-C
Appearance		White or almost white crystalline powder	Conforms	Conforms	Conforms
Crystal form		Crystal form A	Crystal form A	Crystal form A	Crystal form A
Identification	IR	Infrared spectrum corresponds to that of RS.	Conforms	Conforms	Conforms
	HPLC	The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that of the Standard preparation,	Conforms	Conforms	Conforms
Water		≤ 0.5%	0.298%	0.269%	0.265%
Heavy Metals		< 10 ppm	Conforms	Conforms	Conforms
Related substances	Imp. A	≤ 0.2%	0.02%	0.01%	ND
	Any other imp.	≤ 0.1%	0.07%	0.08%	0.1%
	Total imp.	≤ 0.5%	0.12%	0.19%	0.18%
Residual solvents	Ethanol	≤ 5000ppm	35ppm	76 ppm	26 ppm
	toluene	≤ 890 ppm	ND	35 ppm	17 ppm
Assay		98.0%-102.0%	101.7%	100.6%	101.3%

(2) Discussion of Process Parameters and Their Control Range at Kilo Scale

All process parameters excepting the reaction temperature in Step III at kilo production are well within the pre-determined range. The reaction temperature in Step III was proposed at room temperature for kilo batch production based on the results from small scale, however, the quality of IBR03 was so bad and the level of the impurity A was 6.09%. In order to decrease the impurities in IBR03, we tried to lower the reaction temperature to 6°C. The results from the next two kilo batches production demonstrated that the reaction temperature can directly decrease the levels of impurities of IBR03, impurity A decrease from 6.09% to 0.28%, and the other impurities can also decrease to some extent. Therefore, the reaction temperature in Step III is proposed as a critical process parameter and its range is proposed to be 5±2°C.

Table 3.2.S.2.6-13 Impurities under different reaction temperature of Step III

Batch number	IRB02-KG-A	IRB02-KG-B	IRB02-KG-C
Reaction temp.	24 ºC	6 ºC	6 ºC
Unknown impurity	1.28%	0.81%	0.68%
Impurity A	6.09%	0.28%	0.29%
Impurity 1 (RRT ≈ 0.95)	0.08%	0.06%	0.10%
Impurity 2 (RRT ≈ 1.52)	0.06%	0.04	0.12%
Impurity 3 (RRT ≈ 0.79)	0.02%	0.02	0.02%
IRB03	91.28%	97.75%	97.50%

(3) Conclusion

The results demonstrated that the manufacturing process of Irbesartan could be scale-up to kilo scale with some process parameter adjusted, and the quality of Irbesartan is well within the pre-determined range.

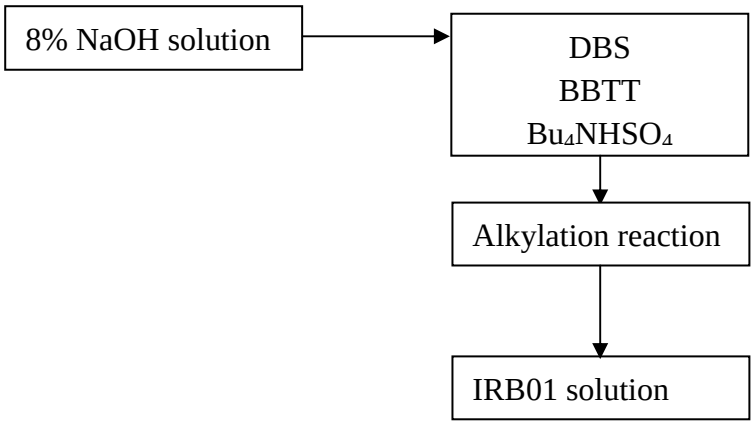
3.2.S.2.6.2 Scale-up to pilot plant

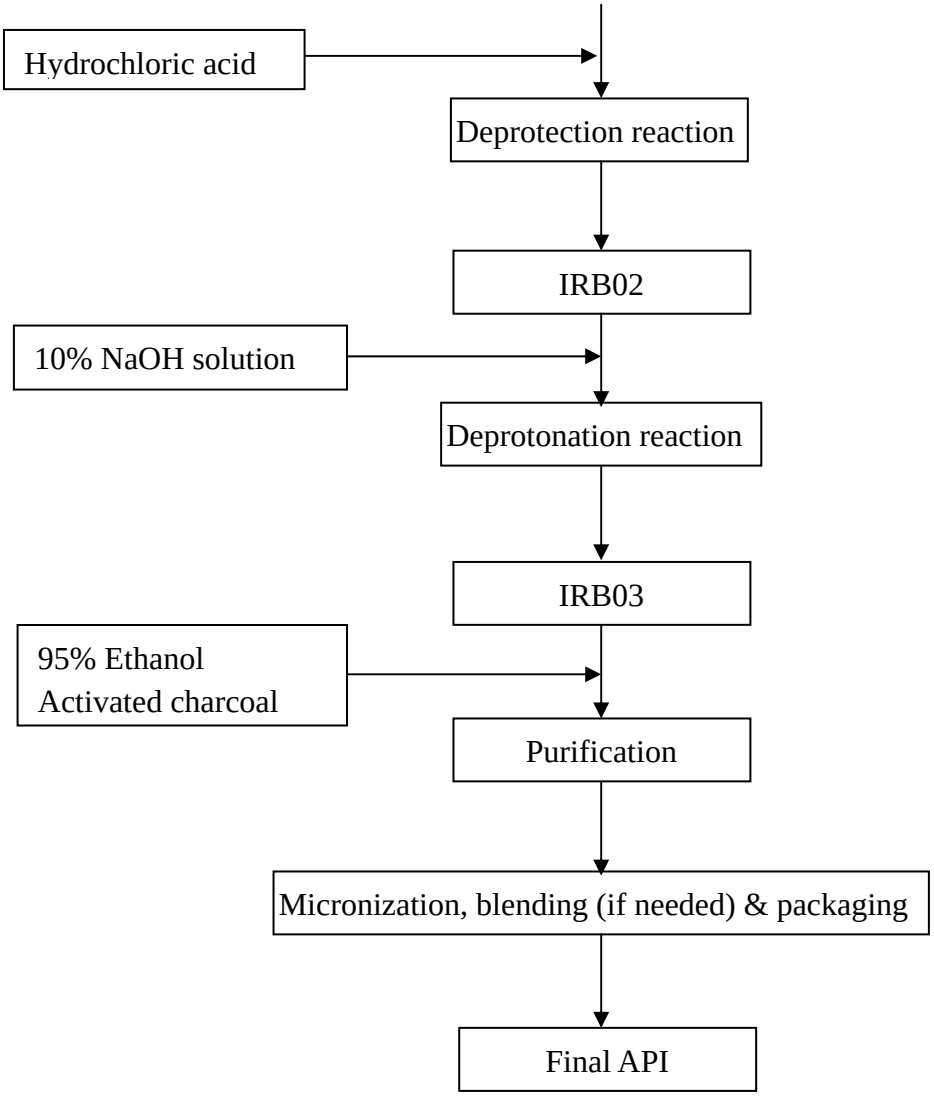
Based on the process parameters described in Table 3.2.S.2.6-15, two consecutive batches (Lot No.: IRB01-120001 and IRB01-120002) at pilot-scale were conducted in pilot plant. During scale-up, the following aspects were investigated:

- Confirm the industrial feasibility of the manufacturing process at larger scale;
- Confirm the ability to produce consistently the qualified Irbesartan;
- Further confirm the critical process parameters (CPP) and their control ranges;
- Investigate the suitability of manufacturing equipments.

1. Brief Description of the Manufacturing Process

The brief flow chart of Irbesartan manufacture is presented below based on the kilo-scale manufacturing process:





Some process parameters used in the small scale batches were adjusted before or during the scale-up pilot stage based on the prior knowledge and our understanding on the manufacturing process to accommodate the scale-up batch size. The main process parameters used in small scale and pilot-scale are listed below.

Table 3.2.S.2.6-14 Process Parameters in Kilo and Pilot Scale

Process Parameters (*Critical Process Parameters)	Kilo Scale	Pilot-scale	Discussion
Step I: Alkylation reaction			
*Reaction temp.	85± 2°C	85± 2°C	No change
Addition temp.	≤ 40°C	≤ 40°C	No change
Cooling temp.	50± 5°C	30± 5°C	The smell of toluene will be terrible at high temperature. So the cooling temperature is adjusted which cannot affect the quality of product.
Step II: Deprotection reaction			
Addition temperature	≤ 50°C	25± 2°C	The same reason as above
Reaction temp.	65± 5°C	First: 35 ± 2°C Then:50 ± 2°C Finally: 65 ± 2 °C	To obtain IRB02 with smaller particle size which can reduce the possibility of impurities included in IRB02.
Step III: Deprotonation reaction			
*Reaction temp.	5± 2°C	5± 2°C	No change
*pH	2.7-3.2	2.7-3.2	No change
Addition temp.	< 10°C	< 10°C	No change
Step IV: Purification			
Cooling temp.	First: 78~80°C Then: 40± 5°C Finally: 0± 5°C	First: 78~80°C Then: 40± 5°C Finally: 0± 5°C	No change
*Crystallization temp.	0± 5°C	0± 5°C	No change
Step V: Drying			
*Drying temp.	60± 5°C	60± 5°C	No change

2. Results of Scale up to Pilot Plant

In order to further confirm the manufacturing process at larger scale, two pilot-scale productions were conducted in pilot plant and the results are presented below.

Step I: Alkylation reaction

Process Description

DBS, BBTT and Bu_4NHSO_4 are dissolved in toluene, and the resulting solution is kept below 30 °C. Then 8% sodium hydroxide solution is added dropwise under 40 °C.

The resulting solution is heated gradually to 85 ± 2°C. The reaction is monitored with HPLC for end point of un-reacterd BBTT is not more than 0.5%.

After the reaction is complete, the reaction mixture is cooled down to 30 ± 5°C and allowed to stratify. The organic layer is collected and used in the next step directly.

Pilot Production Results of IRB01

The critical process parameter (CPP), process parameter (PP) and in-process control (IPC) used in the pilot production of IRB01 according the above mentioned process are presented in Table 3.2.S.2.6-15 and the test results of IRB01 are presented in Table 3.2.S.2.6-16.

Table 3.2.S.2.6-15 Process Control Results of IRB01 in Pilot Scale

Batch No.	Quantity of BDS	CPP	PP		IPC
		Reaction temp.	Addition temp.	Cooling temp.	Reaction Completeness
IRB01-120001	60 kg	84.1-85.0°C	17.6-25.3°C	34.8°C	0.054%
IRB01-120002	60 kg	83.2-85.2°C	23.1-26.1°C	32.7°C	0.071%
Acceptance criteria		85± 2°C	≤ 40°C	30± 5°C	BBTT< 0.5%

Table 3.2.S.2.6-16 In-Process Control of IRB01 Reaction Solution in Pilot Scale

Batch No.	IRB01	Maximum impurity
IRB01-120001	89.9%	2.6%
IRB01-120002	91.3%	2.4%

As IRB01 is not isolated from the reaction solution, it is not tested. However, the test result of IRB02 demonstrated that the manufacturing process of IRB01 can be sacle-up and is suitable for synthesis of Irbesartan.

Step II: Deprotection reaction

Process Description

To the IRB01 solution from last step, hydrochloric acid is added with and the reaction mixture is heated gradually 65 ± 2°C.

The completion of the reaction is determining by TLC for end-point of un-reacted IRB01 is not more than 0.02%.

The reaction mixture is cooled to 25 ± 5°C and centrifuged. The filter cake is then stirred in solvents of toluene-water in suspension at 25 ± 5°C and centrifuged to obtain IRB02.

Pilot Production Results of IRB02

CPP, PP and IPC used in pilot production of IRB02 according the abovementioned process are presented in Table 3.2.S.2.6-17 and the test results of IRB02 are presented in Table 3.2.S.2.6-18.

Table 3.2.S.2.6-17 Process Control Results of IRB02 in Pilot Scale

Batch No.	**Batch size**	**PP**		**IPC**
		Addition temp.	**Reaction temp.**	**Reaction Completeness**
IRB02-120001	126kg	25.0-25.1°C	First: 33.0-36.8°C Then: 48.4-49.5 °C Finally: 63.1-67.0°C	<0.02%
IRB02- 120002	135.50kg	23.0-24.3°C	First: 33.4-36.5°C Then: 48.1-48.8°C Finally: 63.1-63.3°C	<0.02%
Acceptance criteria		25± 2°C	First: 35 ± 2°C Then: 50 ± 2°C Finally: 65 ± 2 °C	IRB01<0.02%

Table 3.2.S.2.6-18 Test Result of IRB02 in Pilot Scale

Batch No.	**Impurities**		**Total impurities**	**IRB02**
	Impurity 2-9 (RRT ≈ 0.95)	**Impurity 2-11 (RRT ≈ 1.52)**		
IRB02-120001	0.05%	0.06%	3.1%	96.9%
IRB02-120002	0.04%	0.06%	4.0%	96.0%
Acceptance criteria	≤ 0.10%	≤ 0.10%	≤5.0%	≥ 95.0%

The results demonstrated that the manufacturing process of IRB02 can be scale-up to pilot plant and the quality of IRB02 is well within the pre-determined range.

Step III: Deprotonation reaction

Process Description

IRB02 is added into water and the mixture is stirred at 5 ± 2 °C, then sodium hydroxide solution is added dropwise under 10 °C. The resulting solution is stirred at 5 ± 2 °C and then diluted hydrochloric acid is added dropwise to adjust the pH to 2.7~3.2. White precipitate is observed, centrifuged and filtered.

The filter cake is stirred in water at 5 ± 5 °C, and centrifuged, filtered and dried to provide IRB03a.

IRB03a is stirred in anhydrous ethanol at 78 ± 3°C, and 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 to provide IRB03.

Pilot Production Results of IRB03

CPP, PP and IPC used in pilot production of IRB03 according the above mentioned process are presented in Table 3.2.S.2.6-19 and the test results of IRB03 are presented in Table 3.2.S.2.6-20.

Table 3.2.S.2.6-19 Process Control Results of IRB03 in Pilot Scale

Batch No.	**Batch size**	**CPP**		**PP**
		Reaction temp.	**pH**	**Addition temp.**
IRB03-120001	85.25kg	3.3-5.8°C	3.10-3.14	5.4-8.0°C
IRB03-120002	86.80kg	3.0-4.3°C	3.15-3.18	5.6-8.4°C
Acceptance criteria		5± 2°C	2.7-3.2	< 10°C

Table 3.2.S.2.6-20 Test Result of IRB03 in Pilot Scale

Batch No.	**Impurities**			**IRB03**
	Impurity 1 (RRT ≈ 0.95)	**Impurity 2 (RRT ≈ 1.52)**	**Impurity 3 (RRT≈ 0.79)**	
IRB03-120001	0.05%	0.06%	0.05%	97.2%
IRB03-120002	0.05%	0.06%	0.15%	97.3%
Acceptance criteria	≤ 0.10%	≤ 0.10%	≤ 0.10%	≥ 90.0%

The results demonstrated that the manufacturing process of IRB03 can be scale-up to pilot plant and the quality of IRB03 is well within the pre-determined range.

Step IV: Purification

Process Description

IRB03 is decolorized in ethanol in the presence of active charcoal in 78 ± 3 ^{o}C. After the solution becomes clear, it is filtered and the filter cake is rinsed with re-heated ethanol. The filtrate and eluate are combined and cooled gradually 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 (IRB04).

Pilot Production Results of IRB04

PP and IPC used in pilot production of IRB04 according the abovementioned process are presented in Table 3.2.S.2.6-21 and the test results of IRB04 are presented in Table 3.2.S.2.6-22.

Table 3.2.S.2.6-21 Process Control Results of IRB04 in Pilot Scale

Batch No.	**Batch size**	**PP**	**CPP**
		Cooling procedure	**Crystallization temp.**
IRB04-120001	122.79kg	First: 78.1°C Then:38.3~44.0°C Finally:3.0~4.1°C	3.0~4.1°C
IRB04-120002	136.91kg	First: 78.2~78.3°C Then:35.3°C Finally:2.1~2.9°C	2.1~2.9°C
Acceptance criteria		First: 78~80°C Then: 40± 5°C Finally: 0± 5°C	0± 5°C

Table 3.2.S.2.6-22 Test Result of IRB04 in Pilot Scale

Batch No.	**Foreign Matter**
IRB04-1205001	4/g
IRB04-1205002	2/g
Acceptance criteria	≤ 10/g

The results demonstrated that the manufacturing process of IRB04 can be scale-up to pilot plant and the quality of IRB04 is well within the pre-determined range.

Step V: Drying and Mricronization

Process Description

The wet IRB04 is dried at 60 ± 5 ^{o}C under 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 transferred into PE bags.

The dried Irbesartan is grinded by using grinder equipped with an appropriate size sieve. The Irbesartan is collected in PE bags. The product is weighed and marked as IRB05.

Pilot Production Results of IRB05

CPP used in pilot production of IRB05 according the abovementioned process is presented in Table 3.2.S.2.6-23. IRB05 is the final product and the test results of IRB are presented in Table 3.2.S.2.6-24.

Table 3.2.S.2.6-23 Process Control Results of IRB05 in Pilot Scale

Batch No.	**Batch size**	**CPP: Drying temp.**
IRB05-120001	68.1kg	55.6-60.3°C
IRB05-120002	83.7kg	55.8-63.5°C
Acceptance criteria		60± 5°C

Table 3.2.S.2.6-24 Test Result of IRB05 in Pilot Scale

Test			Acceptance criteria	Batch number	
				IRB-1205001	IRB-1205002
Appearance			White or almost white crystalline powder	Almost white crystalline powder	Almost white crystalline powder
Identification	Infrared Absorption		Infrared spectrum is concordant with that of the reference standard	Conforms	Conforms
	HPLC		The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.	Conforms	Conforms
Water			Not more than 0.5%	0.25%	0.28%
Heavy metals			Not more than 0.002%	Conforms	Conforms
Related compounds	Impurity A		Not more than 0.15%	ND	ND
	Any other impurity		Not more than 0.10%	0.05%	0.07%
	Total impurities		Not more than 0.2%	0.05%	0.13%
Assay			98.0%~102.0% (on the anhydrous basis)	99.9%	99.5%
Residue solvents		Ethanol	Not more than 5000 ppm	106 ppm	1392ppm
		Toluene	Not more than 890 ppm	10 ppm	17 ppm
		Benzene	Not more than 2 ppm	0.20 ppm	ND

*Detection limit for impurity A is 0.02% and for benzene is 0.2ppm

The results demonstrated that the manufacturing process of IRB05 can be scale-up to pilot plant and can produce Irbesartan with quality well within the pre-determined range.

3.2.S.2.6.3 Summary of Submission Batches Production

Based on the results of the pilot productions, three submission batches of Irbesartan API were manufactured under GMP conditions and placed in stability studies. The information about the submission batches are presented below.

3.1 Planed In-process Controls for Submission Batch Production

The planned in-process controls (control strategy) for the manufacture of submission batches are summarized in Tables 3.2.S.2.6-25~26 and are the same as those in pilot production except in-proceess control of water content. The study showed in patent

US5629331A[2] showed water can affect the crystal form of Irbesartan, so the test of water content is added into in-process control of IRB03 and IRB05 to make sure IRB03 and IRB05 generated in crystal form A as we need. The analytical procedures for the in-process control are described under *Section 3.2.S.2.4.2* of this dossier.

Table 3.2.S.2.6-25 Planned In-Process Controls for Submission Batch Production: Critical Process Parameters and Acceptance Criteria

Processes	Critical Process Parameters	Acceptance Criteria
Step I: Alkylation reaction	Reaction temperature	85 ± 2°C
Step III: Deprotonation reaction	Reaction temperature	5 ± 2°C
	pH value	2.7 ~ 3.2
Step IV: Purification	Crystallization temperature	0 ± 5°C
Step V: Drying and Micronization	Drying temperature	60 ± 5°C
Step VI: Blending and Packing	Blending time	20 ± 1 min

Table 3.2.S.2.6-26 End Point Monitoring Plan for Submission Batches Production: In-process Control (IPC)

Process	Control and Acceptance Criteria	Analytical Method
Step I: Alkylation reaction	Un-reacted BBTT < 0.5%	HPLC
Step II: Deprotection reaction	Unreacted IRB 01 ≤ 0.02%	TLC
Step III: Deprotonation reaction	Water content of IRB03a <10.0%	Karl Fischer
	Water content IRB03 <6.0%	Karl Fischer
Step V: Drying and Micronization	Water content of IRB05< 0.5%	Karl Fischer
	Residual ethanol in IRB05 <5000 ppm	GC

3.2. Information on the Submission Batches of Irbesartan

According to the manufacturing process established in the pilot scale, three consecutive batches of Irbesartan API in production scale are manufactured which are also the submission batches.

Step I: Alkylation reaction

The detailed information on three submission batches including the critical process parameters, process parameter, in-process control are listed in the following table.

Table 3.2.S.2.6-27 Process Control Results of IRB01 in Submission Batches

Batch No.	BDS	CPP	PP		PP
		Reaction temp.	Addition temp.	Cooling temp.	Reaction Completeness
IRB01-120006	60kg	83.0-86.0°C	20.1-20.6°C	33.7°C	0.033%
IRB01-120007	60kg	83.9-85.0°C	20.5-28.0°C	34.2°C	0.091%
IRB01-120008	60kg	83.5-85.5	19.0-22.9°C	30.4°C	0.0295%
Acceptance criteria		85± 2°C	≤ 40°C	30± 5°C	BBTT <0.5%

IRB01is not isolated and not tested, but the test result of IRB02 will demonstrate IRB01 is qualified for the next step.

Step II: Deprotection reaction

The detailed information on three submission batches including the critical process parameters, process parameter, in-process control and the test results of IRB02 are listed in the following tables.

Table 3.2.S.2.6-28 Process Control Results of IRB02 in Submission Batches

Batch No.	Batch size	PP		IPC
		Addition temp.	Reaction temp.	Reaction Completeness
IRB02-120006	137.10kg	26.2-26.7°C	First: 35.1-35.3°C Then: 50.1-50.6 °C Finally: 65.0-65.3°C	<0.02%
IRB02-120007	134.80kg	25.3-26.2°C	First: 33.0-37.0°C Then: 48.2-51.5C Finally: 63.0-65.6°C	<0.02%
IRB02-120008	154.75 kg	25.4-25.9°C	First: 34.6-36.3°C Then: 51.2-51.8C Finally: 66.7-67.1°C	<0.02%
Acceptance criteria		25± 2°C	First: 35 ± 2°C Then: 50 ± 2°C Finally: 65 ± 2 °C	IRB01<0.02%

Table 3.2.S.2.6-29 Test Result of IRB02 in Submission Batches

Batch No.	Impurities		Total impurities	IRB02
	Impurity 2-9 (RRT ≈ 0.95)	Impurity 2-11 (RRT ≈ 1.52)		
IRB02-120006	0.03%	0.05%	3.73%	96.27%
IRB02-120007	--	0.06%	3.56%	96.44%
IRB02-120008	0.03%	0.03%	4.0%	96.00%
Acceptance criteria	≤ 0.10%	≤ 0.10%	≤10.0%	≥ 95.0%

The results showed that the final established manufacturing process of IRB02 is stable and can consistently produce the qualified IRB02. The process is appropriate for the commercial batch production.

Step III: Deprotonation reaction

The detailed information on three submission batches including the critical process parameters, process parameter, in-process control and the test results of IRB03 are listed in the following tables.

Table 3.2.S.2.6-30 Process Control Results of IRB03 in Submission Batches

Batch No.	Batch size	CPP		PP	IPC	
		Reaction temp.	pH	Addition temp.	Water content of IRB03a	Water content of IRB03
IRB03-120006	79.85kg	3.1-3.5°C	3.00-3.01	3.2-3.5°C	0.74%	0.49%
IRB03-120007	78.4kg	3.1-4.9°C	2.93-3.01	4.0-6.0°C	0.32%	0.22%
IRB03-120008	79.40kg	3.0-4.5°C	2.92-3.12	3.9-4.6°C	0.40%	0.22%
Acceptance criteria		5± 2°C	2.7-3.2	< 10 °C	< 10.0%	< 6.0%

Table 3.2.S.2.6-31 Test Result of IRB03 in Submission Batches

Batch No.	Impurities			IRB03
	Impurity 1 (RRT ≈ 0.95)	Impurity 2 (RRT ≈ 1.52)	Impurity 3 (RRT≈ 0.79)	
IRB03-120006	0.02%	0.05%	0.06%	99.6%
IRB03-120007	0.02%	0.06%	0.06%	99.5%
IRB03-120008	0.02%	0.05%	0.06%	99.6%
Acceptance criteria	≤ 0.10%	≤ 0.10%	≤ 0.10%	≥ 90.0%

The results showed that the final established manufacturing process of IRB03 is stable and can consistently produce the qualified IRB03. The process is appropriate for the commercial batch production.

Step IV: Purification

The detailed information on three submission batches including the critical process parameters, process parameter, in-process control and the test results of IRB04 are listed in the following tables.

Table 3.2.S.2.6-32 Process Control Results of IRB04 in Submission Batches

Batch No.	Batch size	PP	CPP
		Cooling procedure	Crystallization temp.
IRB04-120006	119.10kg	First: 76.8°C Then:41.3-45.0°C Finally:-2.1~4.7°C	-2.1~4.7°C
IRB04-120007	123.70kg	First: 78.2°C Then:35.5~39.8°C Finally:-4.9~-1.1°C	-4.9~-1.1°C
IRB04-120008	127.06kg	First: 79.9°C Then:36.6~43.3°C Finally:-1.8~1.2°C	-1.8~1.2°C
Acceptance criteria		First: 78~80°C Then: 40± 5°C Finally: 0± 5°C	0± 5°C

Table 3.2.S.2.6-33 Test Result of IRB04 in Submission Batches

Batch No.	Foreign Matter
IRB04-120006	3/g
IRB04-120007	6/g
IRB04-120008	5/g
Acceptance criteria	≤ 10/g

The results showed that the final established manufacturing process of IRB04 is stable and can consistently produce the qualified IRB04. The process is appropriate for the commercial batch production.

Step V: Drying and Micronization

The detailed information on three submission batches including the critical process parameters and in-process control of IRB05 are listed in the following tables.

Table 3.2.S.2.6-34 Process Control Results of IRB05 in Submission Batches

Batch No.	Batch size	CPP	IPC	
		Drying temp.	Water content	Residual ethanol
IRB05-120006	76.6kg	62.0~65.0°C	0.30%	192ppm
IRB05-120007	75.2kg	56.9~61.6°C	0.32%	676ppm
IRB05-120008	76.8kg	57.2~63.4°C	0.38%	99ppm
Acceptance criteria		60± 5°C	< 0.5%	<5000 ppm

The test results for the final API are listed table below.

Table 3.2.S.2.6-35 Test Result of IRB in Submission Batches

		IRB-1208001	IRB-1208002	IRB-1208003	Acceptance criteria
Impurities	Impurity A	ND*	ND	ND	≤ 0.15%
	Any other impurity	0.06%	0.06%	0.06%	≤ 0.10%
	Total impurities	0.06%	0.06%	0.06%	≤ 0.2%
Residual solvent	Ethanol	39 ppm	3088 ppm	586 ppm	≤ 5000 ppm
	Toluene	ND	ND	ND	≤ 890 ppm
	Benzene	ND	ND	ND	≤ 2 ppm
IRB		99.8%	99.2%	99.8%	99.0~101.0%

*Detection limit for impurity A is 0.02%, and detection limit of toluene is 6ppm, and that of toluene is 0.6072ppm. The results of Irbesartan API could refer to section 3.2.S.4.4 Batch Analyses.

The test results of the final Irbesartan drug substance of three submission batches (please refer *Section 3.2.S.4.4 Batch Analysis*) showed that the final established manufacturing process of Irbesartan is stable and can consistently produce the qualified levofloxacin. The process is appropriate for the commercial batch size.

3.2.S.2.6.4 Container Closure System

The package size for bulk Irbesartan is 15 kg/drum.

The primary packaging material is a food grade, low-density polyethylene (LDPE) bag tightly closed with tamper-evident nylon tie. The primary bag enclosed in a second LDPE bag which is tightly closed in the same way.

The outer is a kraft paper drum sealed with dedicated adhesive tape. Labels are stuck to the exterior surface.

The suitability of the packaging system is justified by the *Container Closure System* in section *3.2.S.6* and *Stability* in section *3.2.S.7*.

3.2.S.2.6.5 Microbiological Attributes

The proposed Irbesartan drug substance is a non-sterile drug substance. The microbiological examination described in Ph.Eur.2.6.12 and Ph.Eur.2.6.13 was performed and the results met the requirements stated in Ph. Eur.5.1.4.

Conclusion:

All the test results of intermediates and API meet their acceptance criteria which are suitably used for synthesis of Irbesartan.

Test results demonstrated that there were no significant differences among the three batches. The manufacturing process is described in section *3.2.S.2.2 Description of Manufacturing Process and Process Controls* of this dossier and the batch information is provided in section *3.2.S.4.4 Batch Analysis* of this dossier. Any further changes to the process will follow the change control procedure required by ICH Q7 and stability tests will be carried out on new batches.

LITERATURE FEFERENCES

[1] Dolitzky et al., Novel Synthesis of Irbesartan. Publish No.:US2005/0176794a, Publish Date: Aug, 11, 2005.

[2]Caron et al., Process for the Preparation of a Tetrazole Derivative in Two Crystalline Forms and Novel the Crystalline Form Thereof. Patent Number: US005629331A, Publish Date: May 13, 1997