3.2.S.3.2 Impurities

3.2.S.3.2.1 Impurity Profile of Irbesartan Drug Substance

The evaluation of impurities in Irbesartan includes organic impurities, inorganic impurities and residual solvents. The impurity profile observed or that are potentially produced in the product manufactured at Yichang Changjiang Pharmaceutical Co., Ltd and their acceptance criteria are presented in Table 3.2.S.3.2-1.

Table 3.2.S.3.2-1 Impurity Profile in Irbesartan

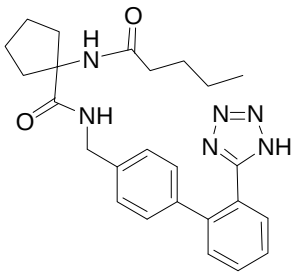
Categories	Impurities		Acceptance Criteria	Analytical Procedure
Organic Impurities	Related substances	Impurity A	≤ 0.15%	Ph.Eur.2.2.29
		Any other impurity	≤ 0.10%	
		Total impurities	≤ 0.2%	
	Impurity B		≤ 10ppm	
Inorganic Impurities	Heavy Metals		≤ 0.002%	Ph.Eur.2.4.8
Residual solvents	Ethanol		≤ 5000 ppm	Ph.Eur.2.2.28
	Toluene		≤ 890 ppm	
	Benzene		≤ 2 ppm	

3.2.S.3.2.2 Organic Impurities

1. List of Potential Related Impurities

The name, structure and origins of potential related impurities, including potential degradation products are provided in Table 3.2.S.3.2-2.

Table 3.2.S.3.2-2 Summary of Potential Related Impurities

Name	Structure	Source
Impurity A		From starting material BDS
Impurity B	N_3^-	From reagent NaN_3 used in synthesis of BBTT

The ranges of the potential related impurities observed in three submission batches are listed in Table 3.2.S.3.2-3.

Table 3.2.S.3.2-3 Impurities Observed in Three Submission Batches

Tests		Acceptance Criteria	Result		
			IRB-1208001	IRB-1208002	IRB-1208003
Impurity B		≤ 10 ppm	ND*	ND	ND
Related substances	Impurity A	≤ 0.15%	ND	ND	ND
	Any other impurity	≤ 0.10%	0.06%	0.06%	0.06%
	Total Impurities	≤ 0.2%	0.06%	0.06%	0.06%

Note: the detection limits of impurity A and B are 0.02% and 0.4ppm respectively.

Representative chromatograms of Impurity B and related substances are presented in Fig 3.2.S.3.2-1 and Fig 3.2.S.3.2-2. The peaks identification information can be found under *Specificity* of *Validation of HPLC Method for Determination of Related Substances* provided in *Section 3.2.S.4.3 Validation of Analytical Procedures*.

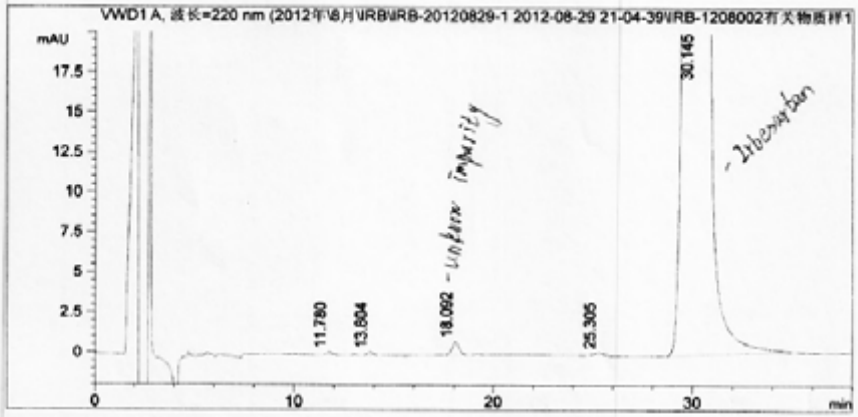
Fig 3.2.S.3.2-1 Representative chromatogram of related compound obtained with Irbesartan

Fig 3.2.S.3.2-2 Representative chromatogram of Impurity B obtained with Irbesartan

数据文件： D:\CHEM32\1\DATA\2012年\8月\IRB\IRB-20120829-1 2012-08-29 21-04-39\IRB-1208002有关物质样1.D
检品信息： IRB-1208002有关物质样1
单针信息： IRB-1208002有关物质样1

报告模板类型： HEC-HPLC-JY0576-性能报告

仪器名称： Agilent1260-液相色谱仪
仪器编号： JY0576 进样量： 10.00 ul
进样日期： 2012/8/30 进样次数： 1次
进样时间： 4:54:08 进样位置： 样品瓶 7
操作者： LL
采集方法： D:\Chem32\1\DATA\2012年\8月\IRB\IRB-20120829-1 2012-08-29 21-04-39\IRB成品有关物质.M
分析方法 D:\CHEM32\1\METHODS\厄贝沙坦有关物质.M



信号相关：

信号： VWD1 A, 波长=220 nm

保留时间 min	峰高 mAU	峰面积 mAU*s	塔板数	分离度	拖尾因子	对称因子	峰面积/%
11.780	0.19	3.95627	7606		1.107	0.9006	0.0109
13.804	0.20	3.92860	12242	3.89	1.061	0.8785	0.0108
18.092	0.84	20.45760	13330	7.61	1.315	0.9859	0.0564
25.305	0.19	5.25777	16688	10.21	0.937	0.9752	0.0145
30.145	938.42	36227.19531	14425	5.41	0.969	1.0648	99.9073

检验人： 复核人：

仪器编号： JY0576 Page 1 of 1

Fig 3.2.S.3.2-1 Representative chromatogram of related compounds obtained with Irbesartan

HEC R&D CENTER 2012-09-05 11:17:02

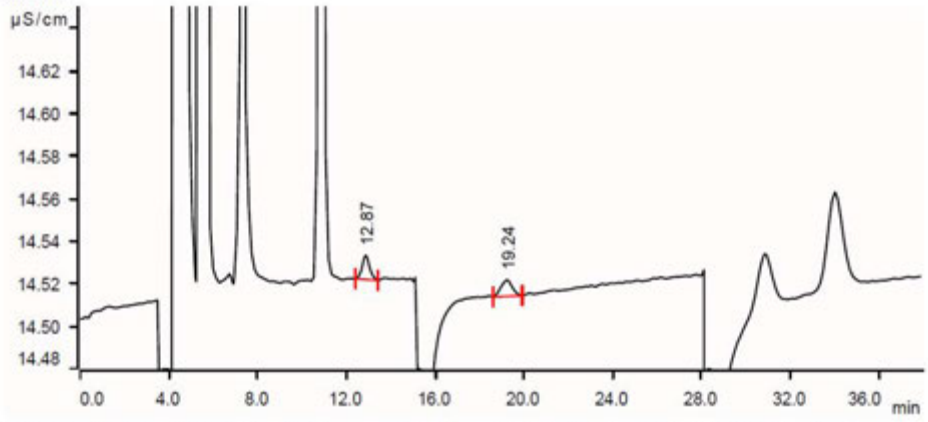
Sample data

Ident	IRB-1208002-1
Sample type	Sample
Determination start	2012-09-05 00:04:49 UTC+8
Method	N3
Operator	

Anions

Data source	Conductivity detector 1 (Ion chromatograph)	
Channel	Conductivity	
Recording time	38.0	min
Integration	Automatically	
Column type	DIONEX IonPac AS10-250/4.0	
Eluent composition	NaN3 eluent - 7.5mmol/LNa2CO3+10%ACN	
Flow	0.800	mL/min
Pressure	13.19	MPa
Temperature	-----	°C

Anions



Component name	Retention time min	Area (µS/cm) x min	Height µS/cm	Resolution	Asymmetry	Theoretical plates
	12.873	0.004344	0.011364	8.625	1.114	7942
	19.240	0.004528	0.007741	invalid	1.022	7336

Page 1 of 1

Fig 3.2.S.3.2-2 Representative chromatogram of Impurity B obtained with Irbesartan

2. Discussion of Origins of Organic Impurities

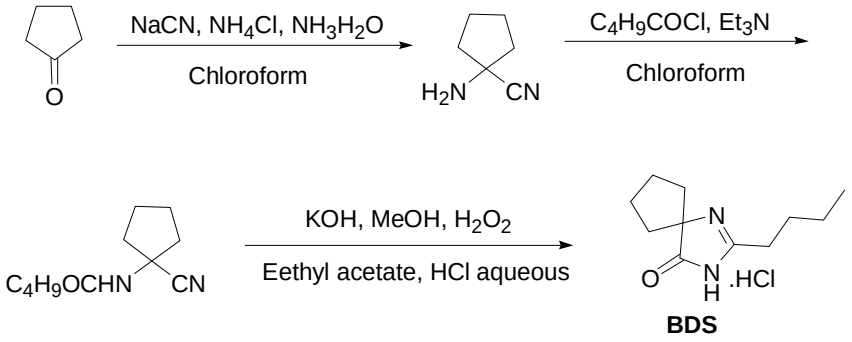
2.1 Potential Process Impurities

2.1.1 Potential Impurities in Starting materials

The starting materials for synthesis of Irbesartan are BDS and BBTT. The impurities in these two starting materials are investigated as followings.

2.1.1.1 Potential impurities in BDS

The synthesis scheme for BDS is listed below:

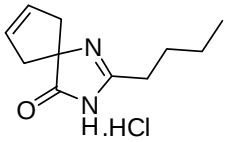
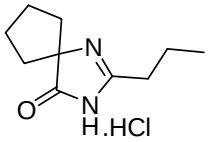
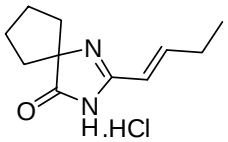
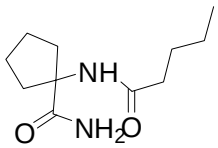


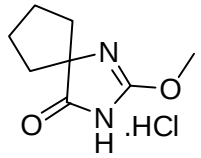
BDS

Potential process impurities in BDS

The name, structure and source of the potential impurities in starting material of BDS are listed in the table below.

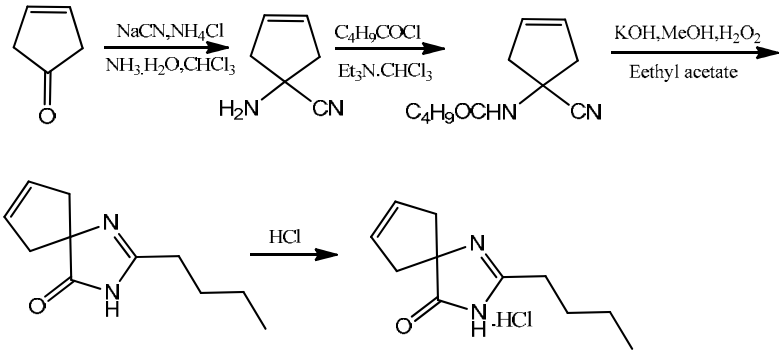
Table 3.2.S.3.2-4 Potential Impurities in BDS

Impurity Code	Structure	Source
Impurity 0-1		Side reaction
Impurity 0-2		Side reaction
Impurity 0-3		Side reaction
Impurity 0-4		Un-reacted intermediate of BDS

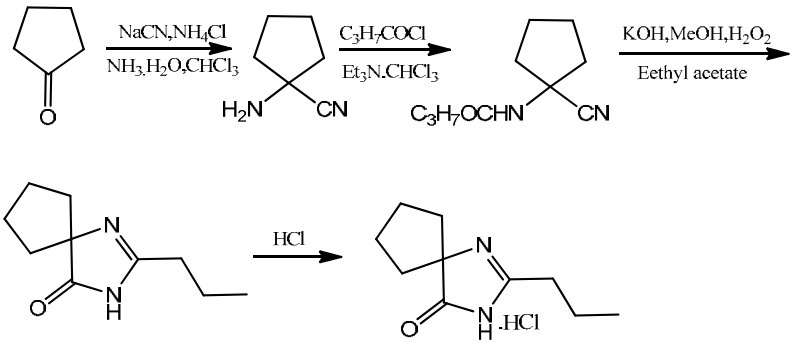
Impurity Code	Structure	Source
Impurity 0-5		Side reaction

Elaboration of potential impurities source in BDS

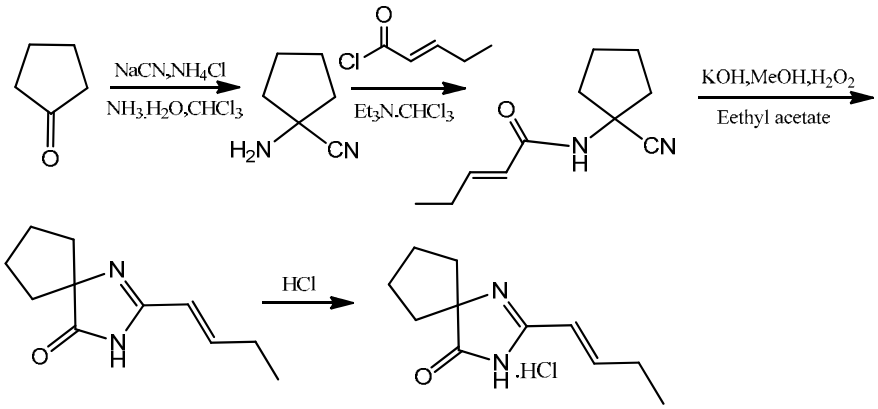
Impurity 0-1: Impurity of cyclopentenone in cyclopentanone participates in the reaction and form impurity 0-1.



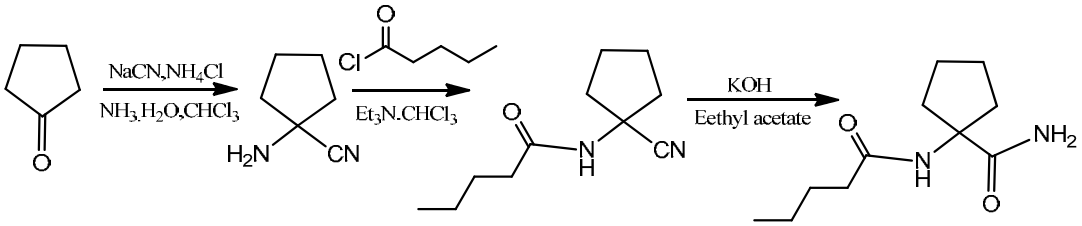
Impurity 0-2: Impurity of *n*-butyryl chloride in valeryl chloride takes part in this reaction and form impurity 0-2.



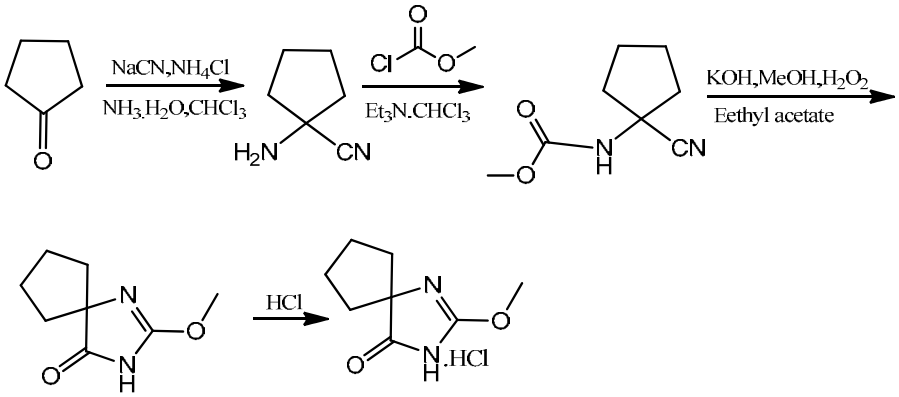
Impurity 0-3: Impurity in valeryl chloride takes part in this reaction and form impurity 0-3.



Impurity 0-4: Un-reacted intermediate of BDS



Impurity 0-5: Impurity of methyl chloroformate in valeryl chloride takes part in this reaction and form impurity 0-5.



The representative LC-MS spectrum to identify the impurity is presented below.

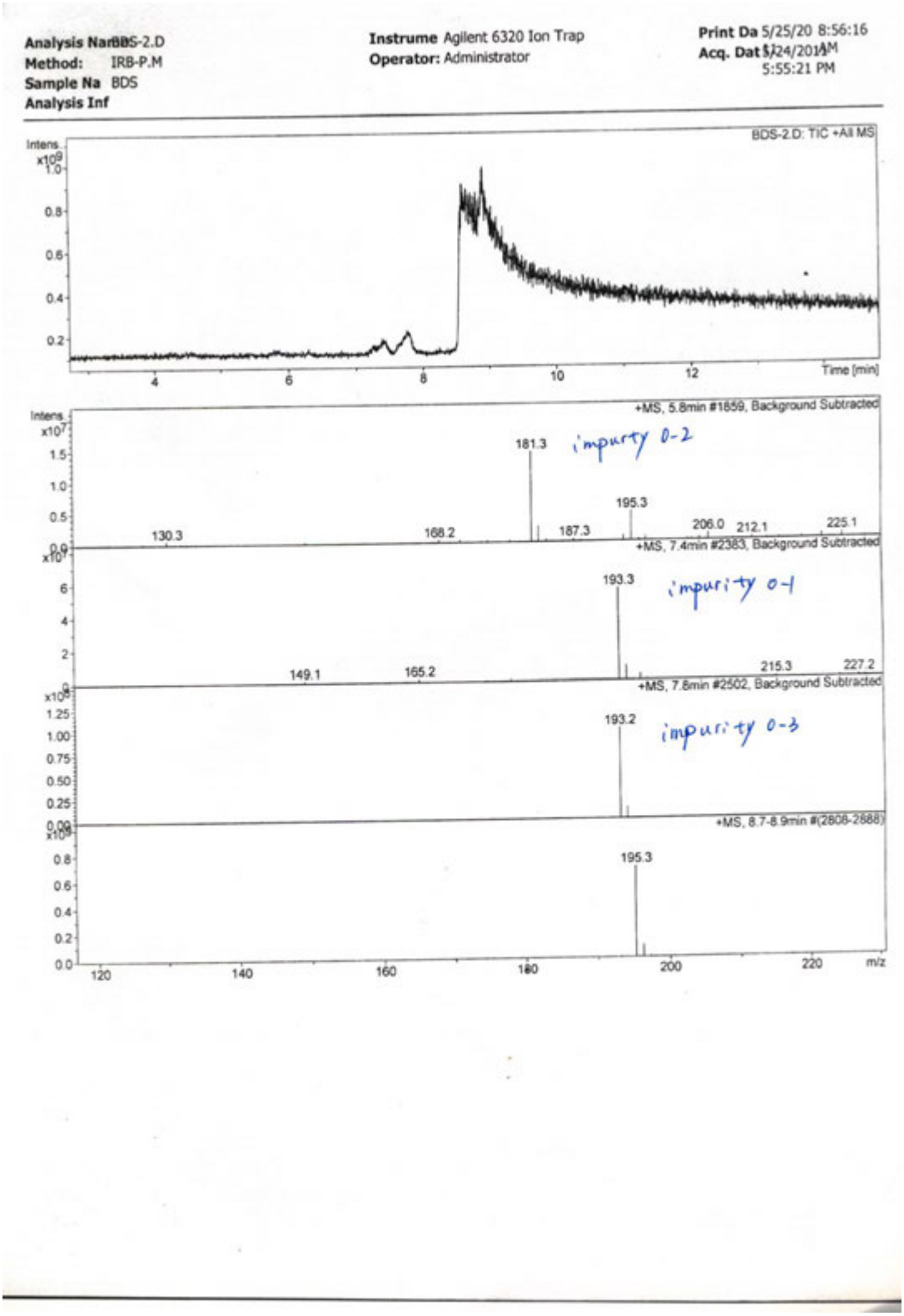


Fig. 3.2.S.3.2-3 LC-MS Spectrum obtained with BDS

Justification of the potential impurities in BDS

Impurities 0-1, 0-2, 0-3, 0-4, 0-5: the structures of these impurities are very close to that of BDS, theoretically, they can take part in the subsequent reactions and corresponding impurities can be removed mostly in step II.

There is tiny quantity of impurities generated from impurities 0-1, 0-2, 0-3, 0-5 in the final product, and they are classified as any other impurity in the drug substance and controlled at not more than 0.10%.

Known impurity A in final product is partly generated by impurity *d*, and its also well controlled in the product with a limit of not more than 0.15%.

And, the impurity limits and test results of BDS listed below demonstrates the impurities in BDS are under good control and the content is very low.

Table 3.2.S.3.1-10 Impurities observed in stating material of BDS

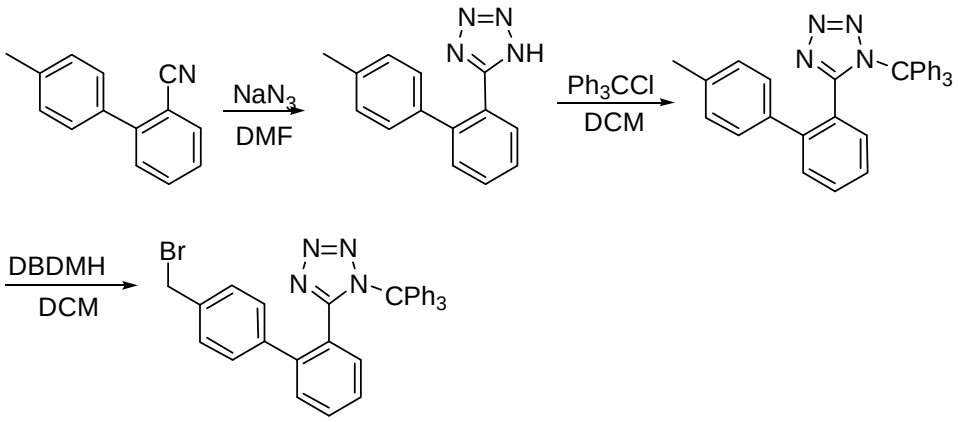
	Acceptance criteria	**Test result**
		Y743-120801
Any impurity	Not more than 0.2%	0.09%
Total impurities	Not more than 1.0%	0.17%

Conclusion

There are 5 potential impurities that may exist in BDS. The test results show all are in very low concentration in the product, and will not affect the quality of final product.

2.1.1.2 Potential Impurities in BBTT

The synthesis scheme for BBTT is listed below:



BBTT

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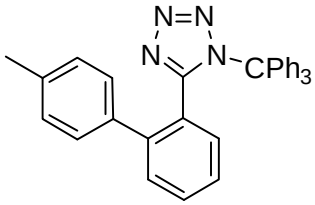
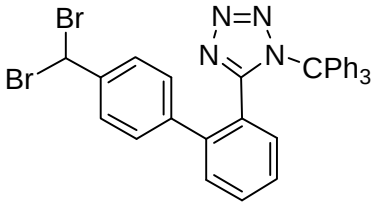
Potential process impurities in BBTT

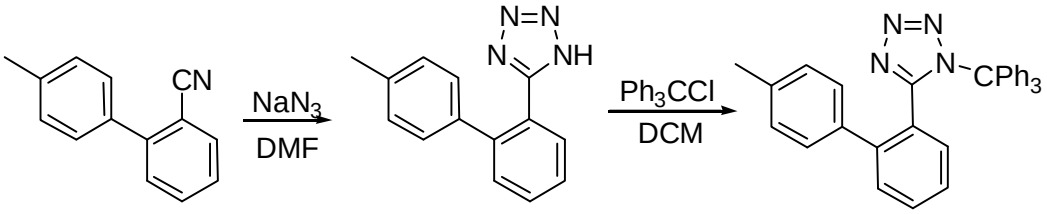
The name, structure and source of the potential impurities in starting material of BBTT are listed in the table below.

Table 3.2.S.3.2-5 Potential Impurities in BBTT

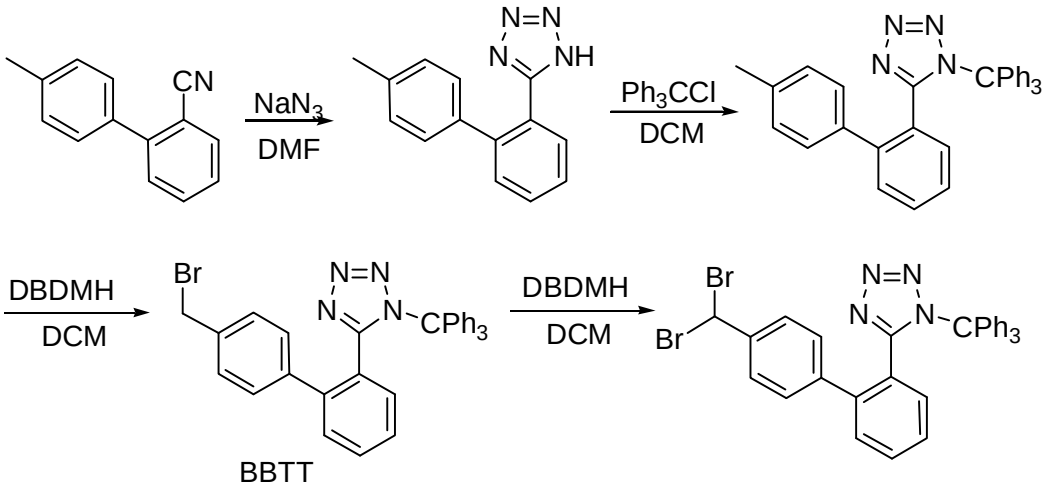
Impurity code	Structure	Source
Impurity 0-6		Side reaction
Impurity 0-7		Side reaction

Elaboration of potential impurities source in BBTT

Impurity 0-6: By-product caused by incomplete bromination



Impurity 0-7: By-product produced by excessive bromination



Structure of Potential impurities supported by NMR:

Analyze the BBTT by HPLC and the results show there are two main impurities in it. These two impurities in BBTT are isolated and analyzed by NMR. The NMR results are concordant and consistent with the structure of the impurities.

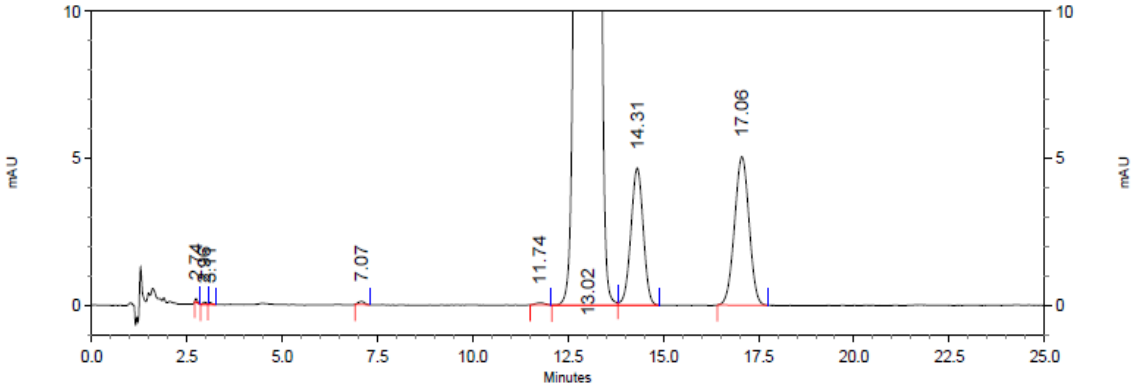
Fig 3.2.S.3.2-4 Representative chromatogram obtained with BBTT

Fig 3.2.S.3.2-5 Representative NMR Spetrum obtained with impurity 0-6 in BBTT

Fig 3.2.S.3.2-6 Representative NMR Spetrum obtained with impurity 0-7 in BBTT

HEC R&D Analysis Report For Irbesartan

Operator:ANALYSIS\zhangqianli **Sample ID:** BBTT-120504 **Injection Vial:** 12 **InjectionVolume:**20UL **Run Time:** 7/16/2012 3:21:26 PM (GMT +08:00) **Analysis Time:** 7/16/2012 3:47:19 PM (GMT +08:00) **Sequence Name**untitled.seq **Method Name:** \\OLSS\EnterprisePath\Projects\Irbesartan RD08007\Method\LC\BBTT\IRB-SM-BBTT-1.met **Date Filename:** \\OLSS\EnterprisePath\Projects\Irbesartan RD08007\Result\LC\1207\120716\2012-07-16 14-51-41 (GMT +08-00).rslt\006 BBTT-120504.dat



DAD: Signal B, 254 nm/Bw:8 nm Ref 360 nm/Bw:100 nm
Results

RT	Name	RRT	Area	Rs(USP)	Asy.	Peak purity	Area%
2.74		0.00	881	0.00	1.63	1.000	0.00
2.96	1	0.00	1030	0.00	0.00	0.922	0.01
3.11		0.00	714	0.82	0.00	0.660	0.00
7.07	2	0.00	2503	17.68	1.12	0.818	0.01
11.74	3	0.00	2483	12.71	1.18	0.634	0.01
13.02	BBTT	0.00	18608972	2.55	0.98	1.000	97.34
14.31	5	0.00	220559	2.22	0.98	1.000	1.15
17.06	6	0.00	280530	4.17	1.00	1.000	1.47
Totals			19117672				100.00

End of Report

Fig 3.2.S.3.2-4 Representative chromatogram obtained with BBTT

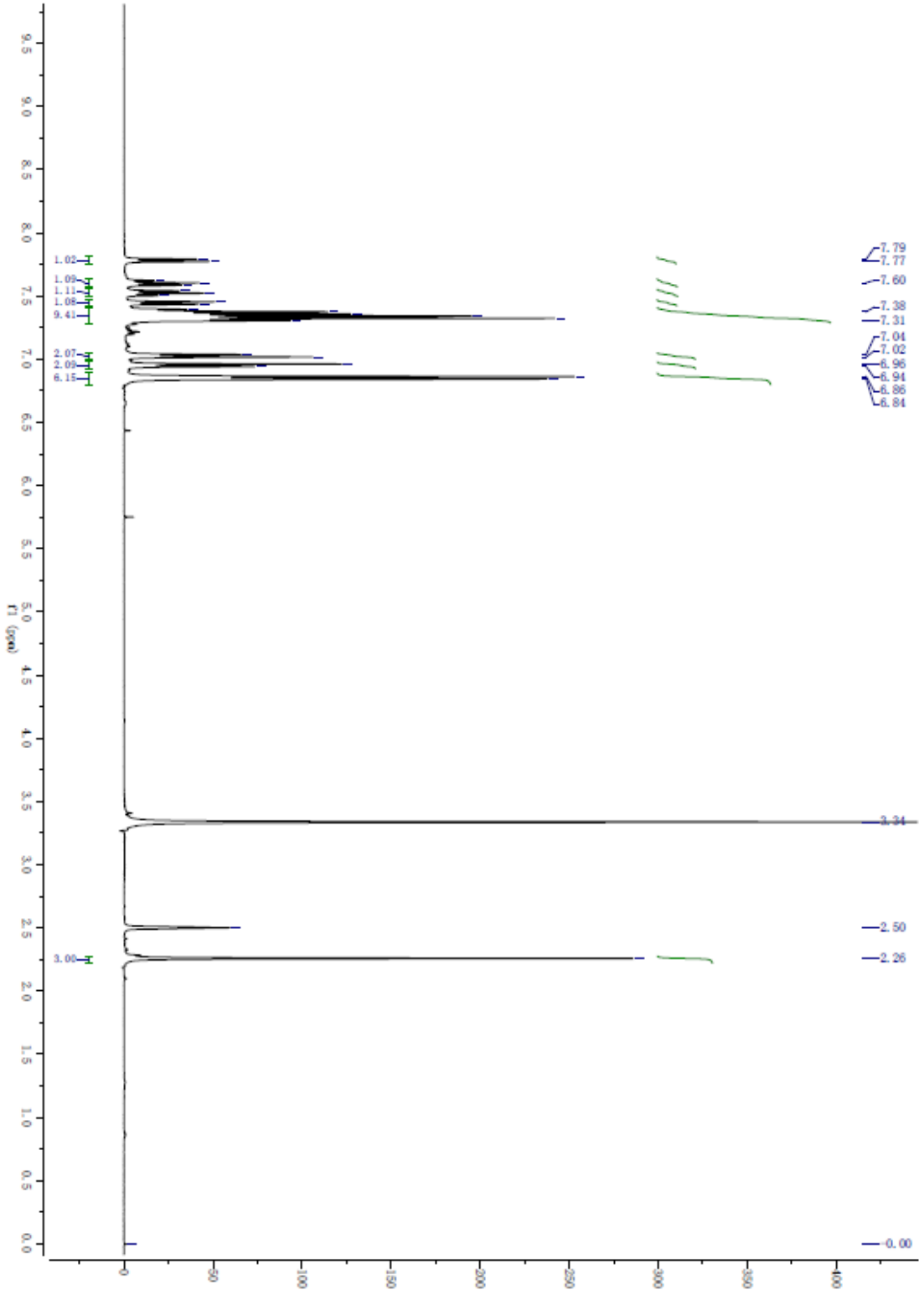


Fig 3.2.S.3.2-5 Representative NMR Spetrum obtained with impurity 0-6 in BBTT

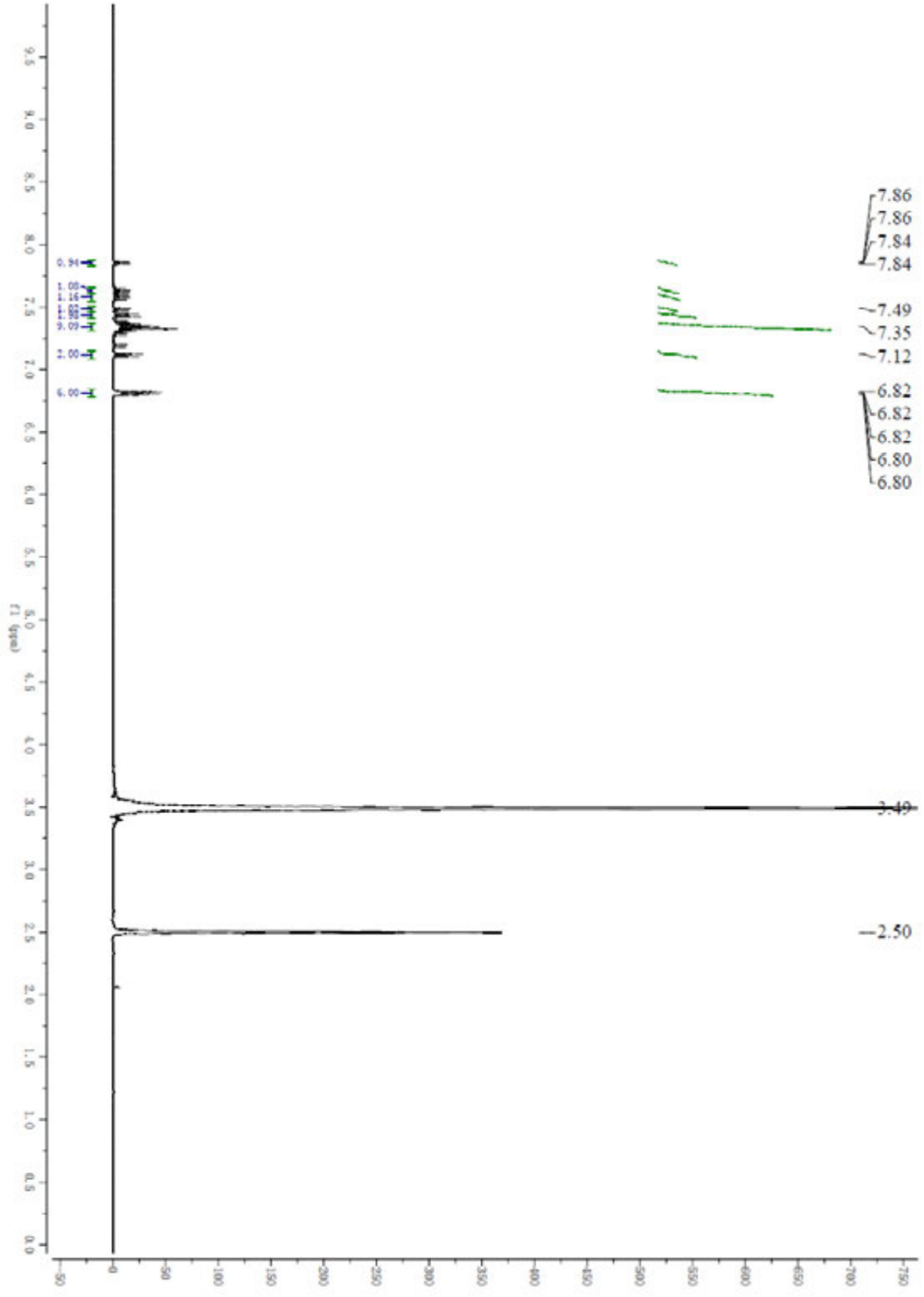


Fig 3.2.S.3.2-6 Representative NMR Spetrum obtained with impurity 0-7 in BBTT

Justification of the potential impurities in BBTT

Impurities 0-6 and 0-7: these two impurities will take part in the subsequent reactions, and the resulted impurities will carry over into IRB02. However, they all can dissolve in water, and will stay in the mother liquid during centrifugation in step II.

To further ensure that impurity 0-6 and impurity 0-7 do not affect the quality of the final product, their limits are defined in the specification of BBTT. The test results are as follows:

Table 3.2.S.3.2-6 Impurities observed in stating material of BBTT

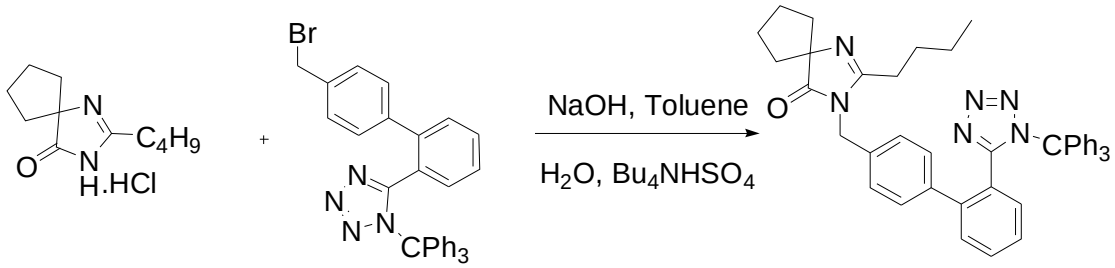
Item	Acceptance criteria	Test result	
		Y744-120302	Y744-12081
Impurity 0-6 (RRT=1.1)	Not more than 2.0%	1.2%	1.1%
Impurity 0-7 (RRT=1.3)	Not more than 2.0%	0.96%	1.3%
Any other impurity	Not more than 0.5%	< 0.05%	0.06%
Total impurities	Not more than 4.0%	2.2%	2.5%

Conclusion

The impurities in BBTT are well identified and controlled. They will not affect the subsequent reaction and the quality of final product.

2.1.2 Potential Impurities in IRB01

The synthesis scheme for IRB01 is listed below:

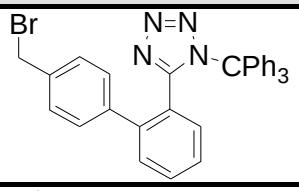
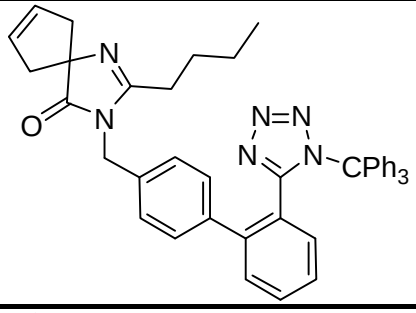
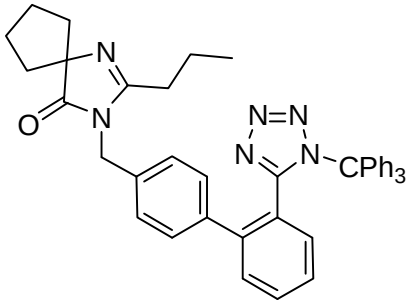
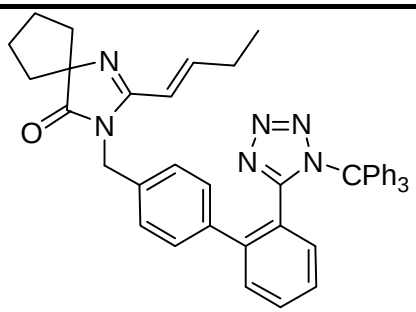
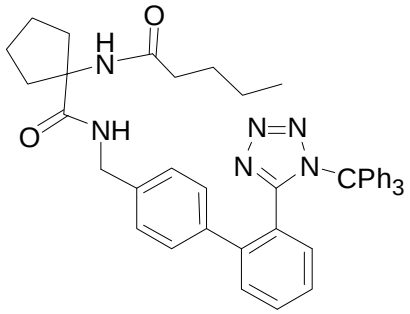


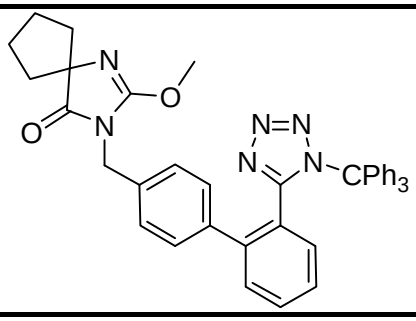
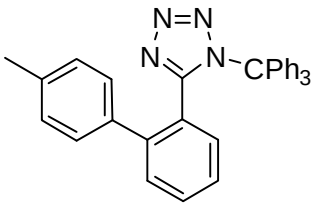
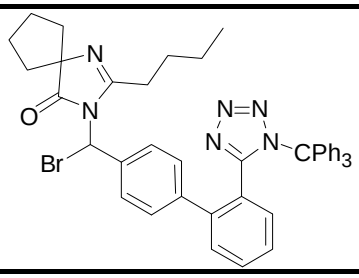
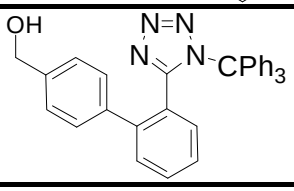
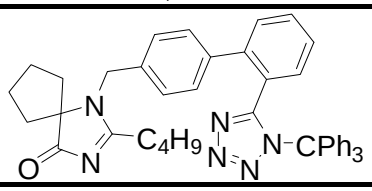
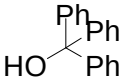
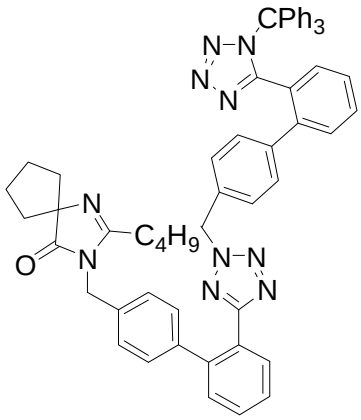
BDS **BBTT** **IRB01**

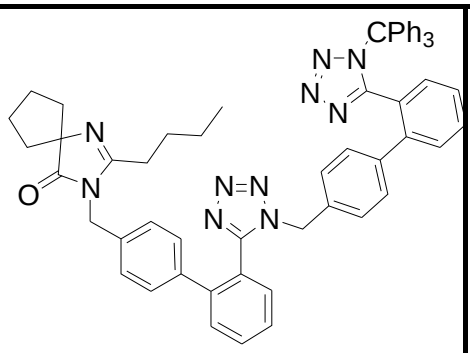
Potential process impurities in IRB01

The name, structure and source of the potential impurities in starting material of BDS are listed in the table below.

Table 3.2.S.3.2-7 Potential Impurities in IRB01

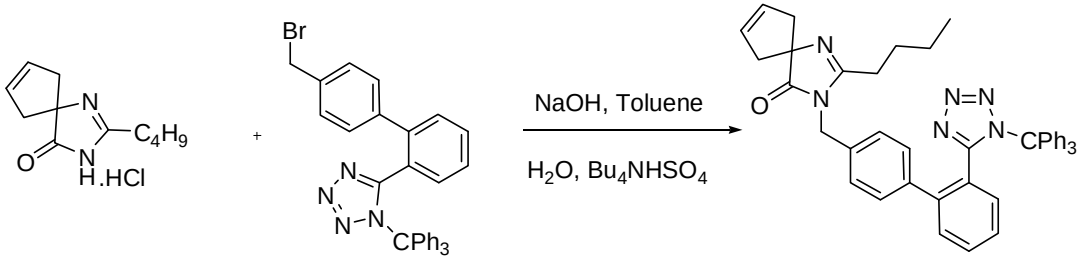
Impurity code	Structure	Source
BBTT		Unreacted reactant
Impurity 1-1		Side reaction
Impurity 1-2		Side reaction
Impurity 1-3		Side reaction
Impurity 1-4		Side reaction

Impurity 1-5		Side reaction
Impurity 0-6		Impurity from BBTT
Impurity 1-7		Side reaction
Impurity 1-8		Side reaction
Impurity 1-9		By-product
Impurity 1-10		Side reaction
Impurity 1-11	 Or:	Side reaction

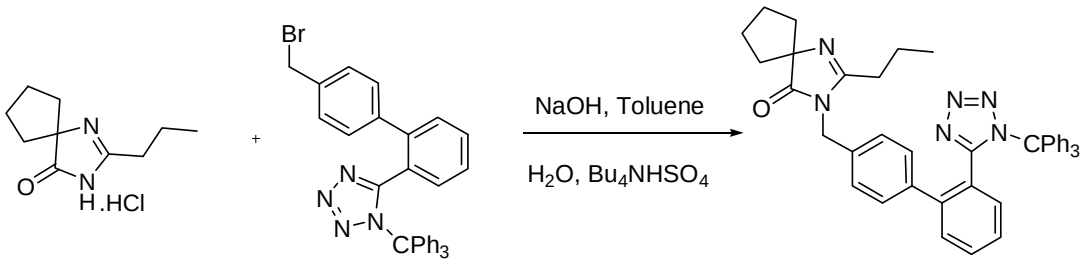
		

Elaboration of potential impurities source in IRB01

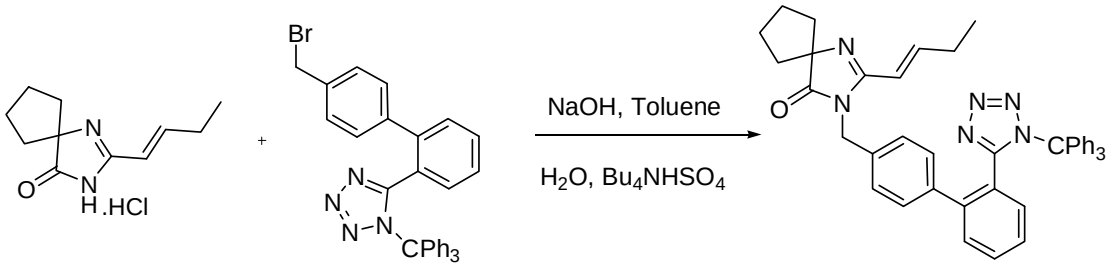
Impurity 1-1: Derivative of impurity 0-1 in this step



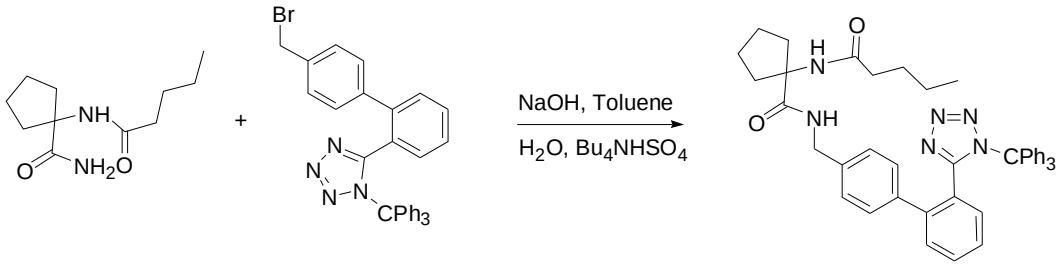
Impurity 1-2: Derivative of impurity 0-2 in this step



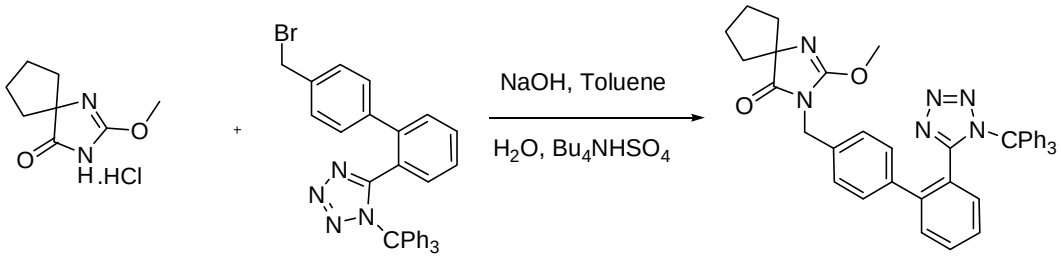
Impurity 1-3: Derivative of impurity 0-3 in this step



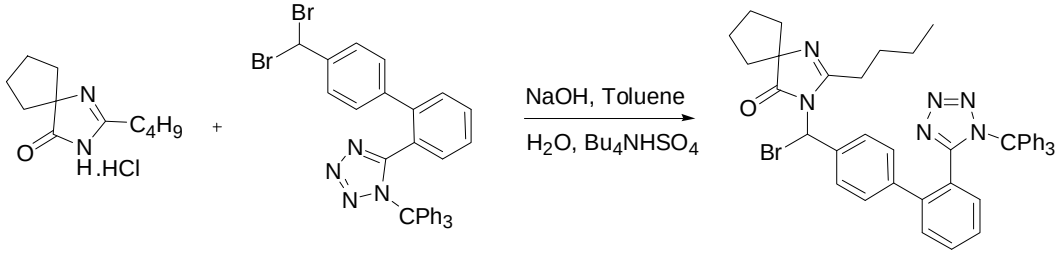
Impurity 1-4: Derivative of impurity 0-4 in this step



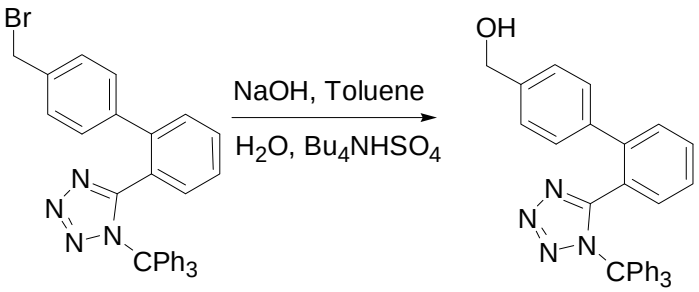
Impurity 1-5: Derivative of impurity 0-5 in this step



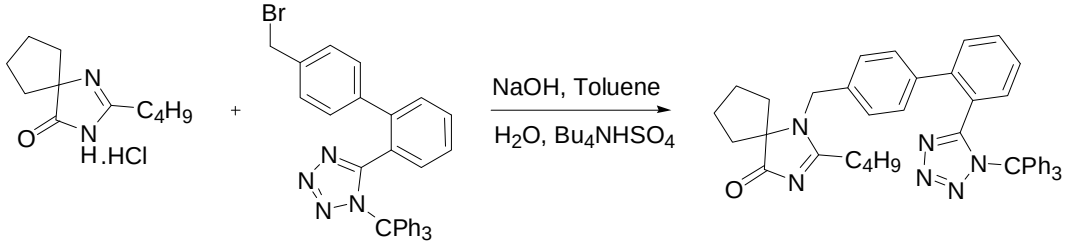
Impurity 1-7: Derivative of impurity 0-7 in this step



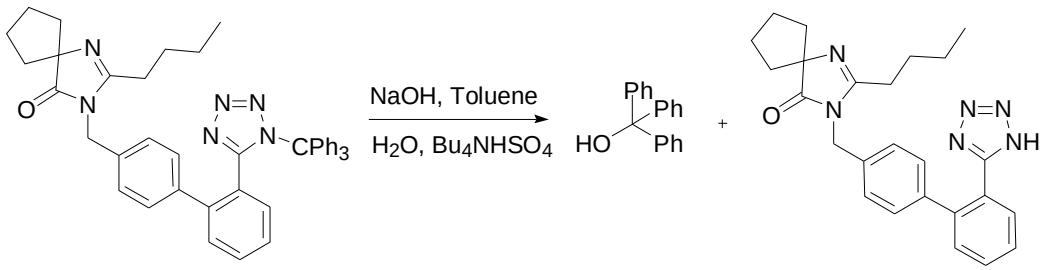
Impurity 1-8: bromo-group of BBTT is substituted by hydroxyl-group in the present of sodium hydroxide, and impurity 1-8 is form.



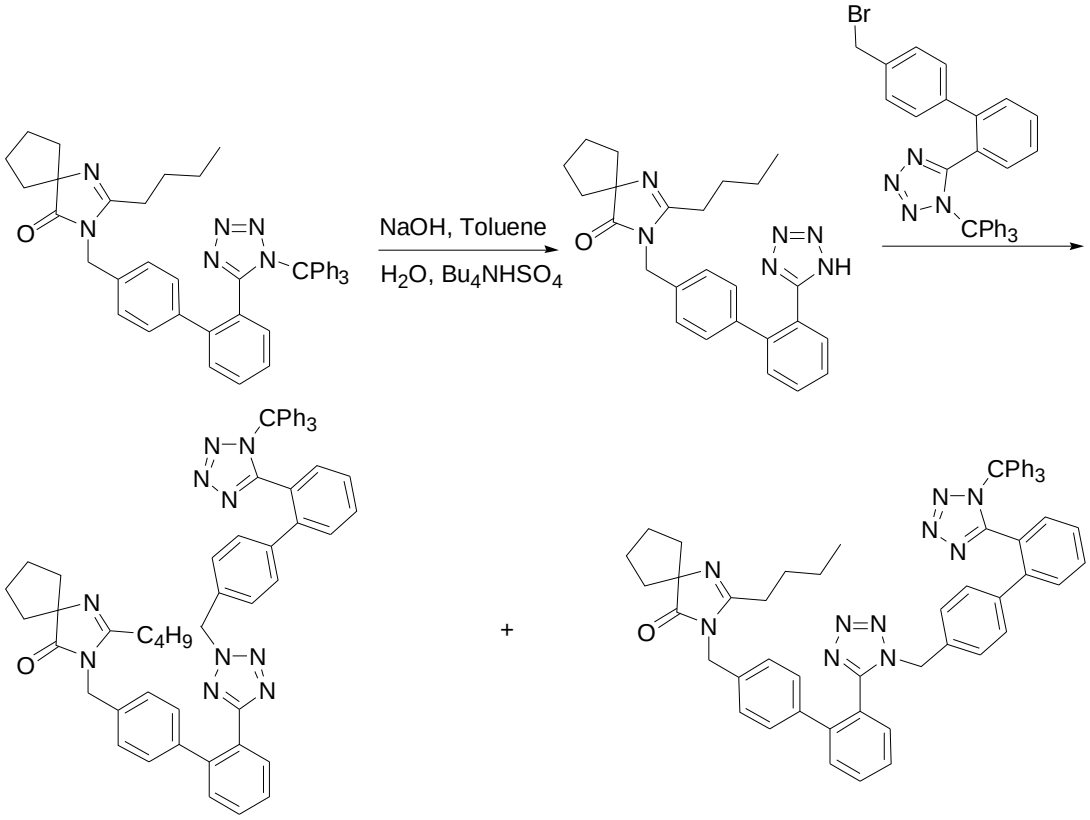
Impurity 1-9: Isomer of IRB01



Impurity 1-10: Protection group removed from IRB01, and the resulting triphenyl methyl group reacts with sodium hydroxide to form this impurity.



Impurity 1-11: Protection group is removed from IRB01, and the resulting product reacts with BBTT to generate this impurity.



Justification of the potential impurities in IRB01

BBTT: it is unreacted reactant. Residual BBTT is controlled to be less than 0.5% in IRB01 for the completeness of reaction. And it can take part in subsequent reaction and the corresponding impurity in IRB02 can well dissolve in toluene and stay in the mother liquid when IRB02 is treated twice with toluene.

Impurities 1-1, 1-2, 1-3, 1-4, 1-5, 1-7: these impurities are respectively generated from impurities 0-1, 0-2, 0-3, 0-4, 0-5, 0-7 in starting materials. The test results of starting materials indicate impurities 0-1, 0-2, 0-3, 0-4, 0-5, 0-7 are very tiny, so their derivatives are much less.

Impurity 0-6: it is carried over from starting material, and it is very tiny. It can take part in the subsequent reaction and its derivative can dissolve in toluene and removed in the

purification of IRB02 by using toluene.

Impurities 1-8, 1-10 and 1-11: these three impurities are generated from side reactions. The chance of these side reactions occurrences is very low, so possibility of the existence of these three impurities is very low.

Impurity 1-9: it is the isomer of IRB01. From the formation mechanism, the product of this reaction is IRB01, isomer of IRB01acarcely exists.

IRB01 is not isolated and used in the next step directly. These potential impurities in IRB01 will carry over into IRB02. They will be removed in the purification of IRB02, and the test results of IRB02 will indicate the impurities in it are very less.

Conclusion

IRB01 is not isolated from the reaction solution and directly transferred to the next step. The specification of IRB01, therefore, is not established and any impurities in it will be tested later in IRB02.

There are 13 potential impurities that may exist in the IRB01 solution, but actually, the HPLC results of the reaction solution of IRB01 indicate that the contents of some impurities are so low that cannot be detected. The existence of these potential impurities will not impact the next step.

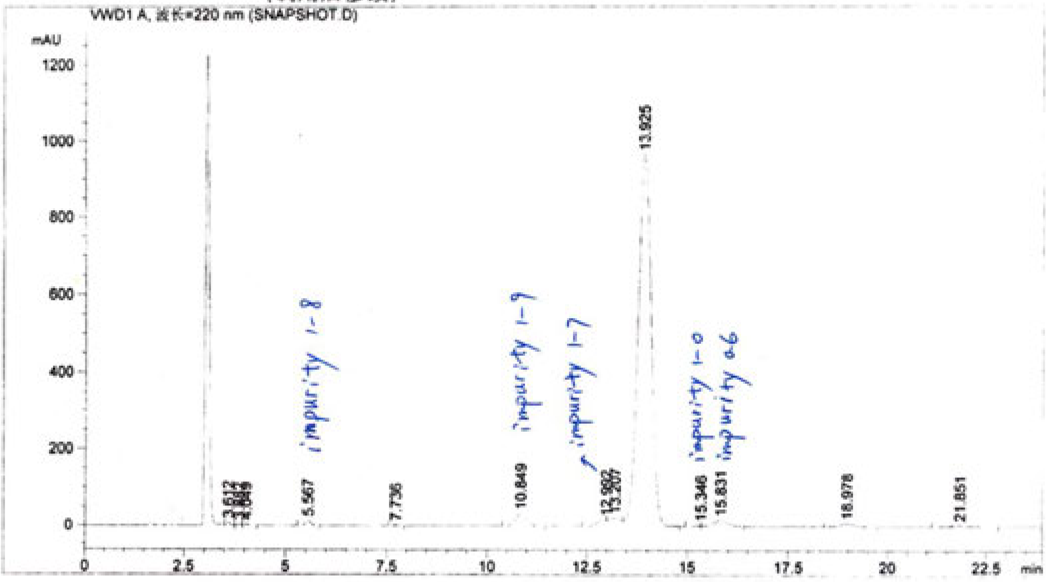
The representative HPLC chromatograms of IRB01 reaction solution and MS spectra to identify the impurities are presented in the following pages.

Fig 3.2.S.3.1-7HPLC chromatogram obtained with IRB01 reaction solution

Fig 3.2.S.3.2-8 MS spectra of impurities obtained with IRB01 reaction solution

数据文件: D:\CHEM32\1\DATA\SNAPSHOT.D
样品名称: IRB01-120007(PV01-01)

操作者 : YC　　　　序列行 : 1
　　　　　　　　　　位置 : 样品瓶 12
进样日期 : 2012-8-11 20:02:49　　　　进样次数 : 1
采集方法 : IRB01有关物质及纯度.M
分析方法 : D:\CHEM32\1\METHODS\AZL含量.M
最后修改 : 2012-8-11 20:37:46 : WSC
(调用后修改)



面积百分比报告

排序 : 信号
乘积因子: : 1.0000
稀释因子: : 1.0000
内标使用乘积因子和稀释因子

IRB01-120007(PV01-01)中控图谱
原料 = 0.09%
[illegible] 2012.08.11

信号 1: VWD1 A, 波长=220 nm

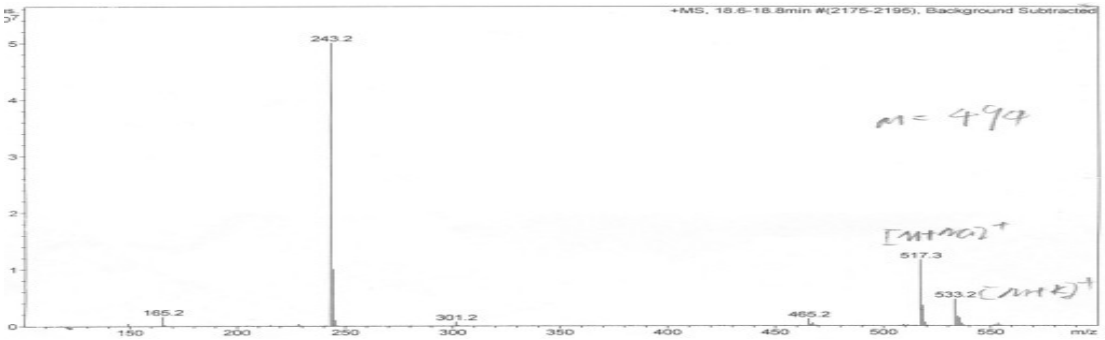
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 mAU *s	峰高 [mAU]	峰面积 %
1	3.612	VV	0.0993	48.04417	7.23445	0.2007
2	3.882	VV	0.1034	20.77916	2.97147	0.0868
3	4.049	VB	0.1261	28.99833	3.33896	0.1211
4	5.567	VB	0.1425	109.42942	12.03600	0.4572
5	7.736	MM	0.2054	18.93880	1.53681	0.0791
6	10.849	BB	0.2934	591.97485	31.31299	2.4731
7	12.992	MF	0.2623	239.01308	15.18546	0.9985
8	13.207	FM	0.3493	433.16080	20.66595	1.8096
9	13.925	VB	0.3512	2.16898e4	964.56586	90.6130
10	15.346	MF	0.2147	21.77345	1.68984	0.0910
11	15.831	FM	0.4186	388.28235	15.46012	1.6221
12	18.978	BB	0.4483	217.30984	7.57452	0.9079
13	21.851	BB	0.5685	129.22212	3.54066	0.5398

仪器 1 2012-8-11 20:37:47 WSC　　　　页 1/2

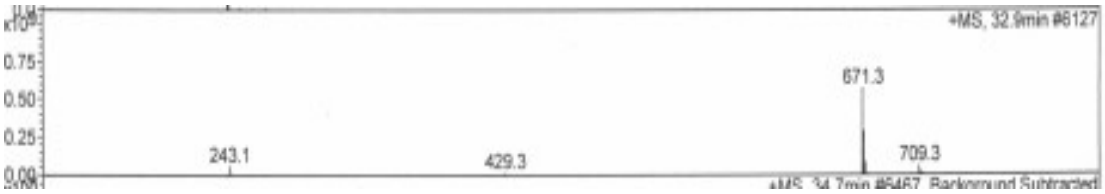
Fig 3.2.S.3.1-7HPLC chromatogram obtained with IRB01 reaction solution

Impurity 1-7:

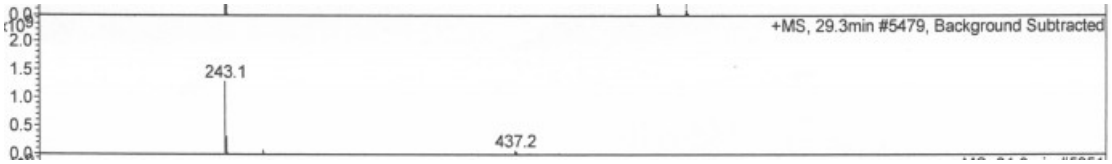
Impurity 1-8:



Impurity 1-9:



Impurity 1-10:



Impurity 1-11:

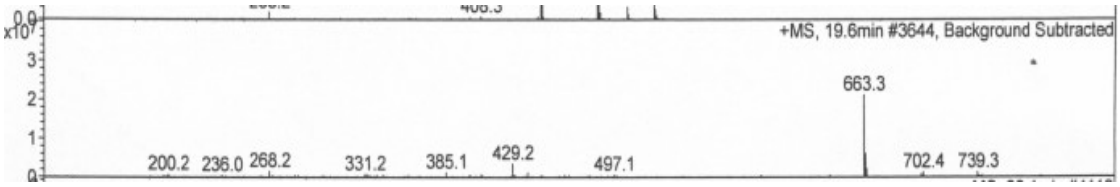
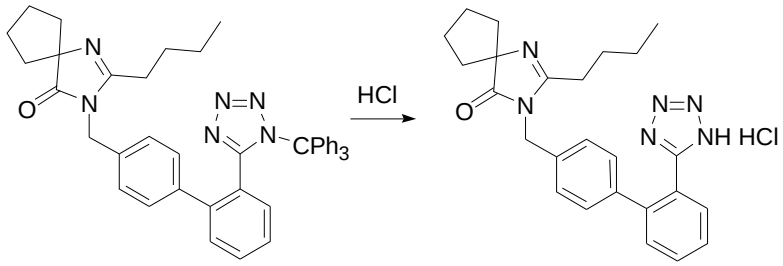


Fig 3.2.S.3.2-8 MS spectra of impurities obtained with IRB01 reaction solution

2.1.3 Potential Impurities in IRB02

The master synthesis scheme for IRB02 is listed below:

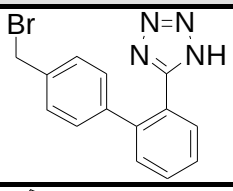
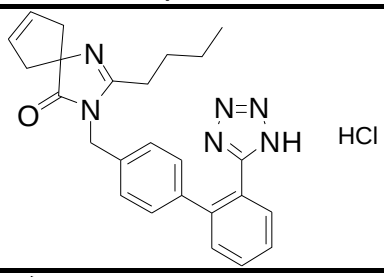
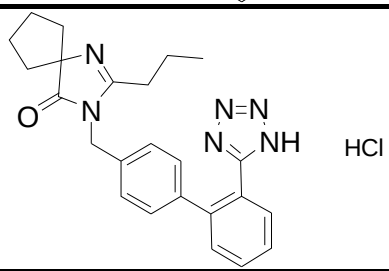
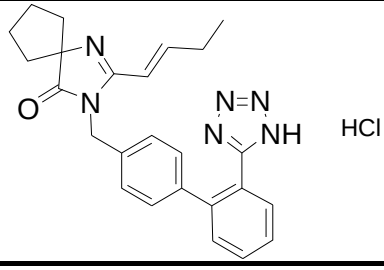


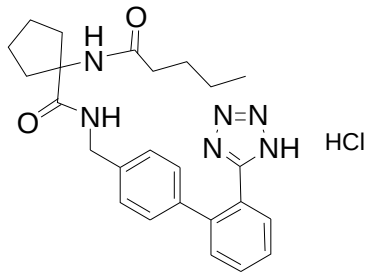
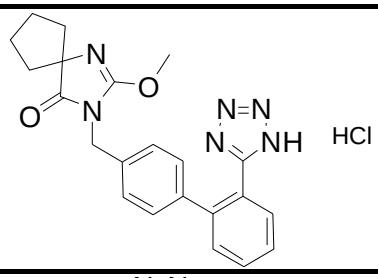
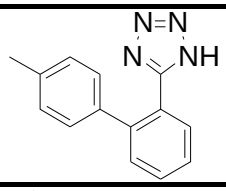
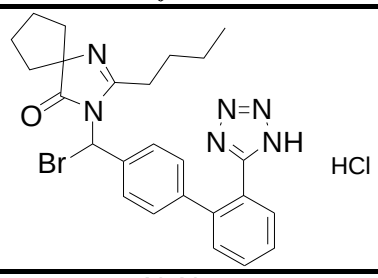
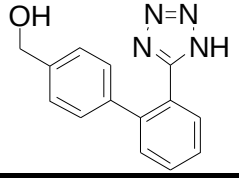
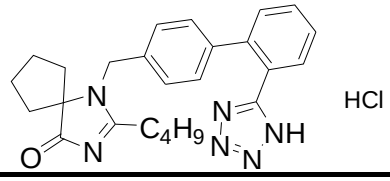
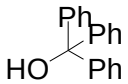
IRB01 **IRB02**

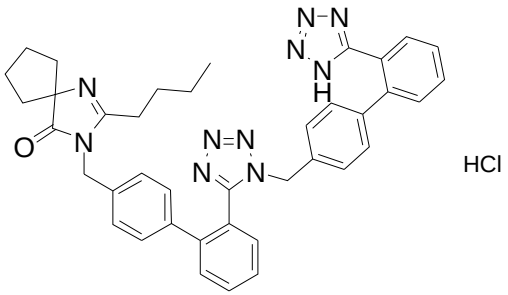
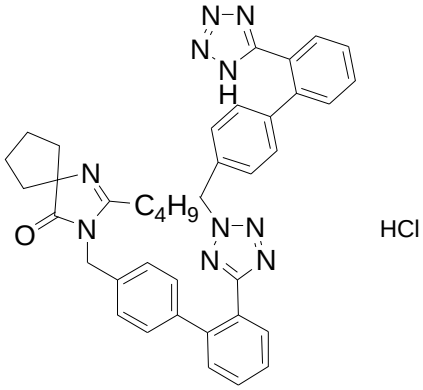
Potential process impurities in IRB02

The name, structure and source of the potential impurities in starting material of IRB02 are listed in the table below.

Table 3.2.S.3.2-8 Potential Impurities in IRB02

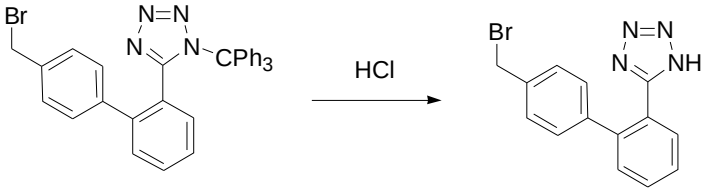
Impurity code	Structure	Source
Deprotected BBTT		Side reaction
Impurity 2-1		Side reaction
Impurity 2-2		Side reaction
Impurity 2-3		Side reaction

Impurity code	Structure	Source
Impurity 2-4		Side reaction
Impurity 2-5		Side reaction
Impurity 2-6		Side reaction
Impurity 2-7		Side reaction
Impurity 2-8		Side reaction
Impurity 2-9		Side reaction
Impurity 1-10		1. by-product 2. impurity from IRB01

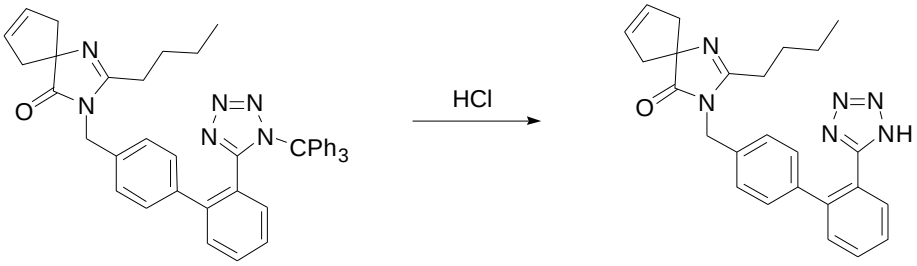
Impurity code	Structure	Source
Impurity 2-11	 Or: 	Side reaction

Elaboration of potential impurities source in IRB02

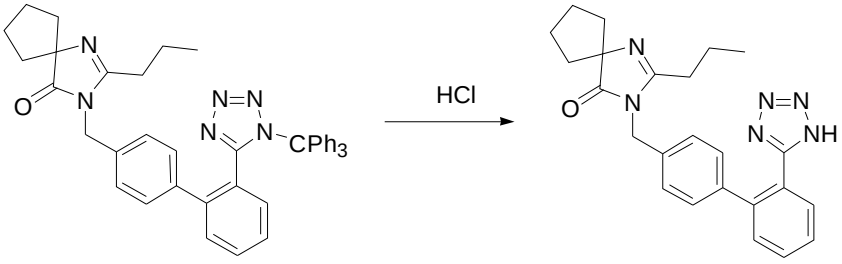
Deprotected BBTT: Derivative from BBTT



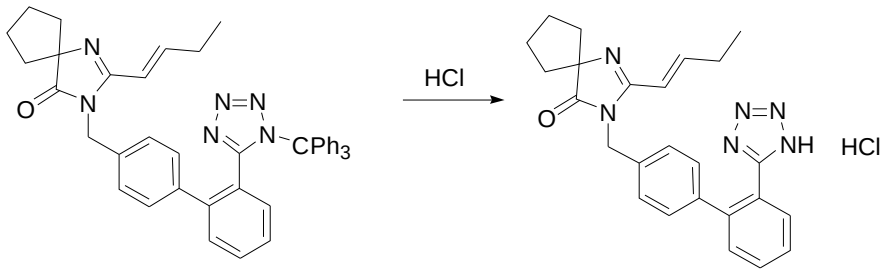
Impurity 2-1: Derivative from impurity 1-1



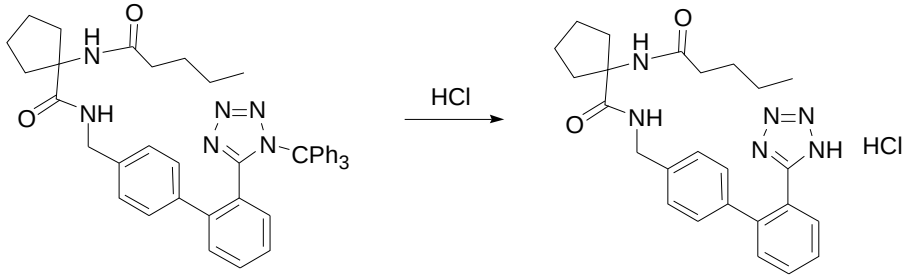
Impurity 2-2: Derivative from impurity 1-2



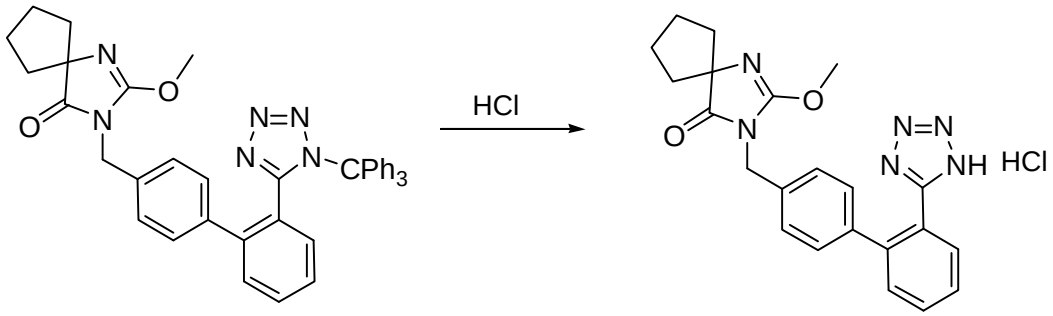
Impurity 2-3: Derivative from impurity 1-3



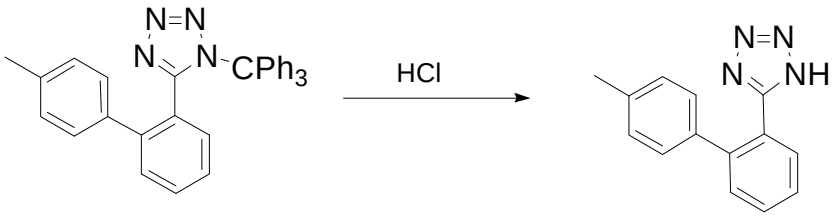
Impurity 2-4: Derivative from impurity 1-4



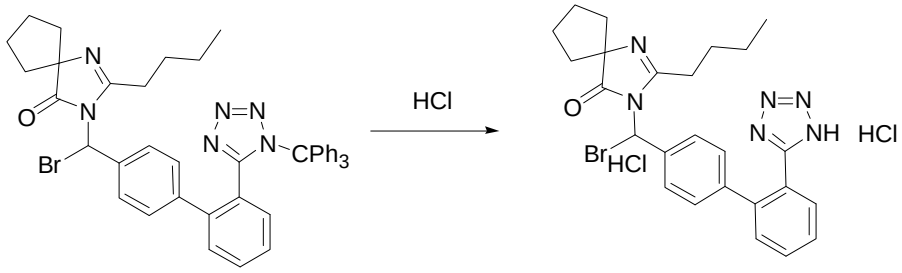
Impurity 2-5: Derivative from impurity 1-5



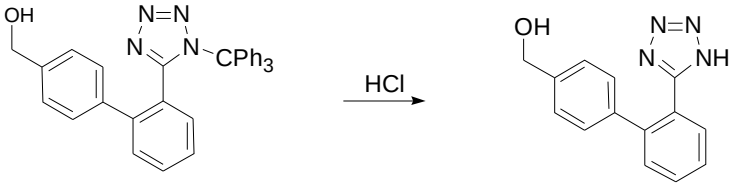
Impurity 2-6: Derivative from impurity 0-6



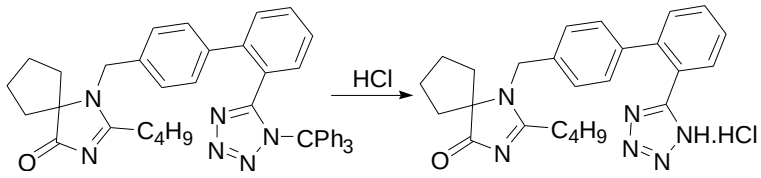
Impurity 2-7*:* Derivative from impurity 1-7



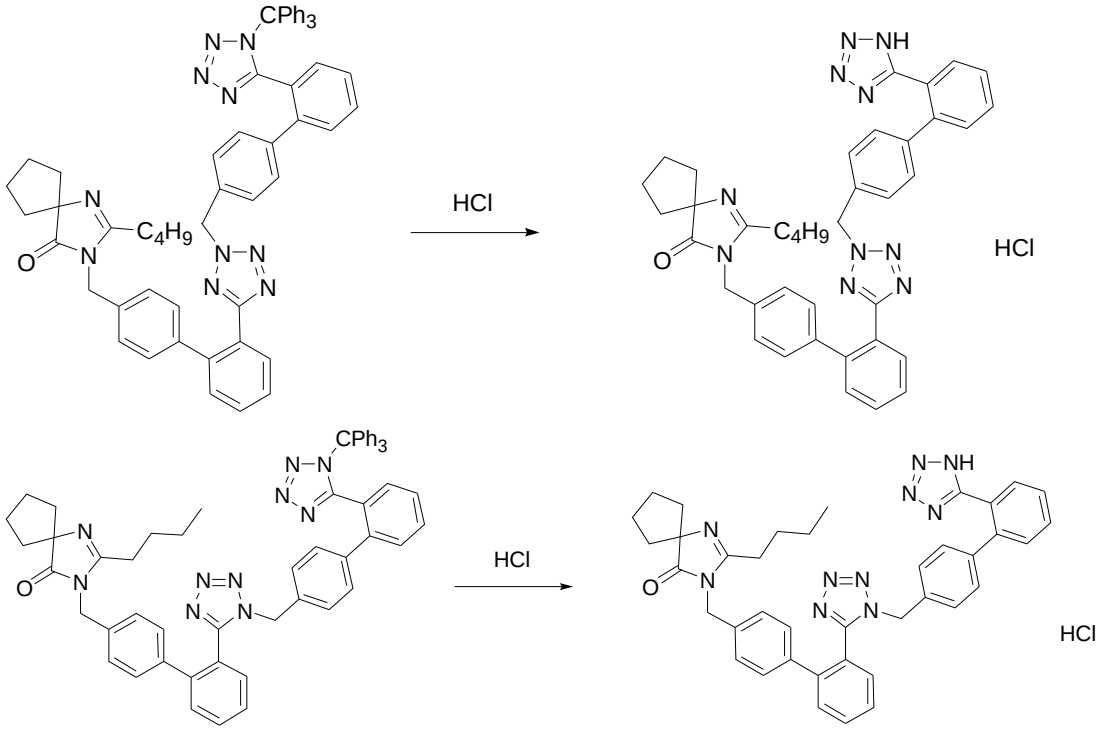
Impurity 2-8: Derivative from impurity 1-8



Impurity 2-9: Derivative from impurity 1-9



Impurity 2-11: Derivative from impurity 1-11



Justification of the potential impurities in IRB02

IRB02 is synthesized in heterogeneous solvents system of water-toluene, and generated in form of hydrochloride salt which cannot dissolve either in water nor toluene. IRB02 can directly precipitate from the solution.

Deprotected BBTT, impurities, 2-8, and 2-6 derived from the BBTT, impurities 1-8, and 0-6 in IRB01. Since BBTT, impurities 1-8, and 0-6 are very tiny, the generated deprotected BBTT, impurities 2-8, and 2-6 will be much less. And they can well dissolve in toluene and stay in the mother liquid when IRB02 is treated twice with

toluene, which ensure the elimination of these impurities.

Impurity 1-10: it is the by-product of this reaction and also an impurity from IRB01. It is relatively more than other impurities in IRB02. However, it can well dissolve in toluene and stay in the mother liquid when IRB02 is isolated by centrifugation. After centrifugation, IRB02 is stirring in toluene which further eliminates all these potential impurities.

Impurities 2-9, 2-7, 2-11, 2-1, 2-2, 2-3, 2-4, 2-5: they are derived from the impurities 1-9, 1-7, 1-11, 1-1, 1-2, 1-3 and 1-4 in IRB01. As impurities 1-9, 1-7, 1-11, 1-1, 1-2, 1-3 and 1-4 are very tiny, the generated impurities 2-9, 2-7, 2-11, 2-1, 2-2, 2-3, 2-4, 2-5 will be even less. And they can dissolve in water and stay in the mother liquid when IRB02 is centrifuged. Part of impurities 2-9, 2-7, 2-11, 2-1, 2-2, 2-3, 2-4, and 2-5 may exist in the form of free alkali, which can well dissolve in toluene and stay in the mother liquid when IRB02 is treated twice with toluene, which ensure the elimination of these impurities.

The test results of IRB02 showed below will further demonstrate the above discussion:

Table 3.2.S.3.2-9 Impurities observed in IRB02

Items	**Acceptance criteria**	**Test result**		
		IRB02-120006	**IRB02-120007**	**IRB02-120008**
Impurity 2-3 (RRT ≈ 0.95)	≤ 0.10%	0.03%	ND	0.03%
Impurity 2-11 (RRT ≈ 1.52)	≤ 0.10%	0.05%	0.06%	0.03%
Total impurities	≤ 10.0%	3.373%	3.56%	4.0%
Purity of IRB02	≥ 90.0%	96.27%	96.44%	96.0%

Conclusion

There are 13 potential impurities that may exist in IRB02 solution, but actually, the HPLC and LC-MS spectrum obtained with IRB02 can only provide signal of impurities 2-9, 2-11, 2-4, and 2-5, the other impurities cannot be detected because they have been removed, or exist with very tiny qualities.

The representative HPLC chromatograms of IRB02 and MS spectra to identify the impurities are presented in the following pages.

Fig 3.2.S.3.2-9 HPLC chromatogram obtained with IRB02

Fig 3.2.S.3.2-10 MS spectra of impurities obtained with IRB02

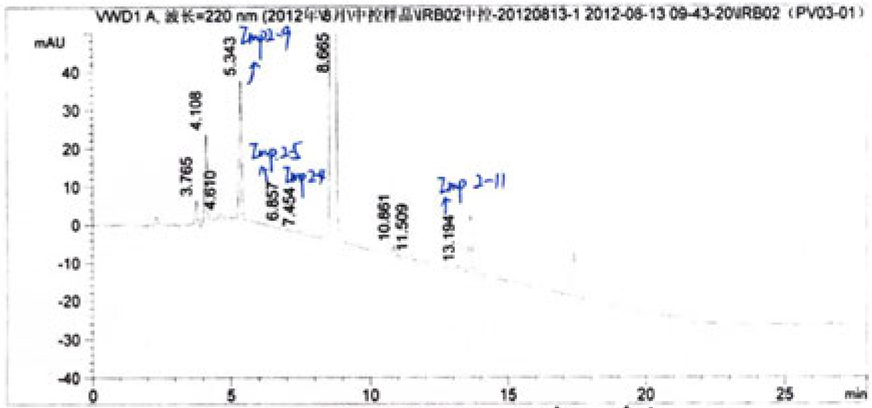
数据文件： D:\CHEM32\1\DATA\2012年\8月\中控样品\IRB02中控-20120813-1 13 09-43-20\IRB02 (PV03-01) -120007.D

检品信息： IRB02 (pv03-01) -120007

单针信息： IRB02 (pv03-01) -120007

报告模板类型： HEC-HPLC-JY0500-性能报告

仪器名称：	Agilent1200-液相色谱仪		
仪器编号：	JY0500	进样量：	5.00 ul
进样日期：	2012-8-13	进样次数：	1次
进样时间：	9:44:34	进样位置：	样品瓶 4
操作者：	SC		
采集方法：	D:\Chem32\1\DATA\2012年\8月\中控样品\IRB02中控-20120813-1 2012-08-13 09-43-20\IRB02.M		
分析方法：	D:\CHEM32\1\METHODS\IRB02.M		



IRB02-120007 (PV03-01)
2012.08.13

信号相关：

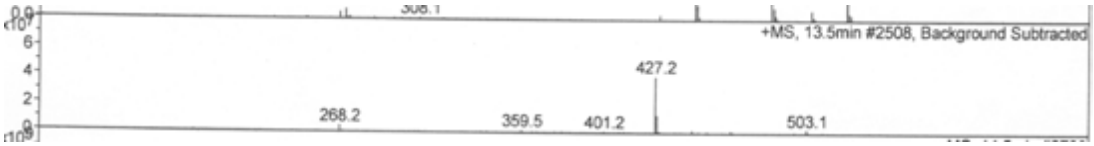
信号： VWD1 A, 波长=220 nm

保留时间 min	峰高 mAU	峰面积 mAU*s	塔板数	分离度	拖尾因子	对称因子	峰面积/%
3.765	5.96	28.67853	14432		1.196	0.881	0.2520
4.108	22.67	124.00728	13415	2.56	1.151	0.885	1.0896
4.610	1.23	6.36854	17712	3.58	1.524	0.904	0.0560
5.343	36.29	202.85559	21680	5.16	1.061	0.909	1.7823
6.857	1.10	7.18392	27644	9.74	0.884	0.787	0.0631
7.454	0.74	4.43083	36201	3.71	0.862	0.791	0.0389
8.665	1643.50	10976.81250	40039	7.33	1.040	0.968	96.4447
10.861	2.56	17.47067	61441	12.59	0.936	0.810	0.1535
11.509	1.04	7.15029	64366	3.63	0.862	0.800	0.0628
13.194	0.90	6.50341	75743	9.02	0.866	0.818	0.0571

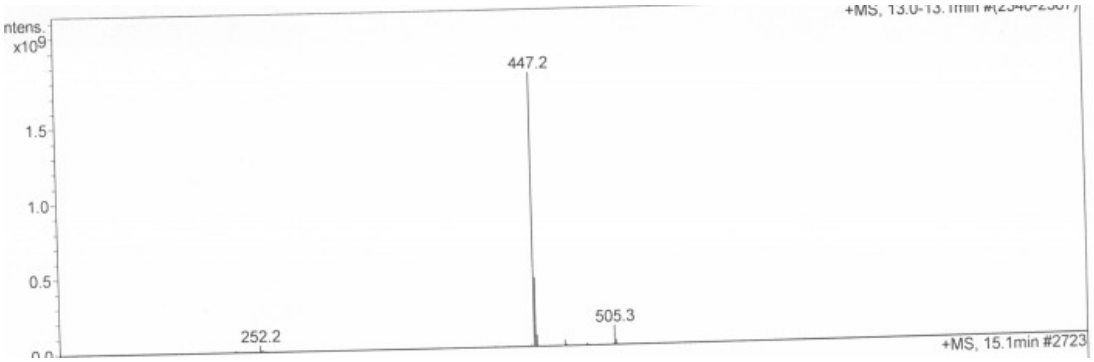
仪器编号： JY0500 14 Page 1 of 1

Fig 3.2.S.3.2-9 HPLC chromatogram obtained with IRB02

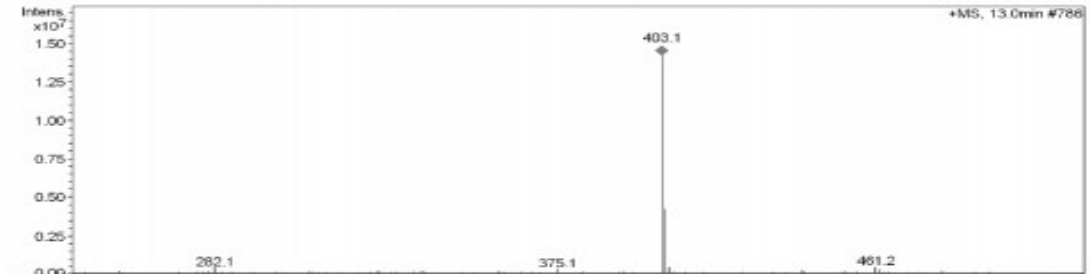
Impurity 2-3:



Impurity 2-4:



Impurity 2-5:



Impurity 2-9:

Impurity 2-11:

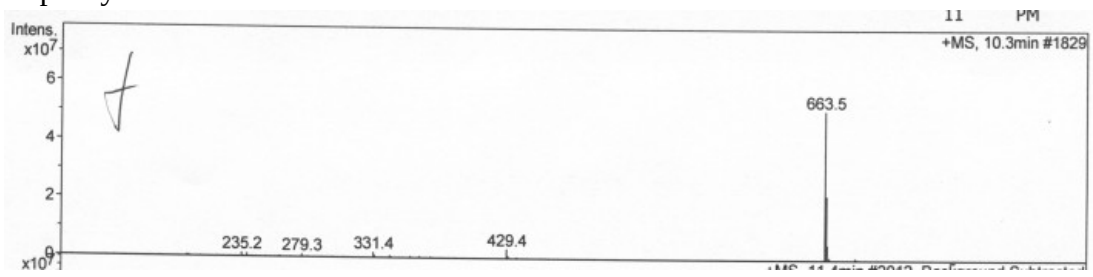
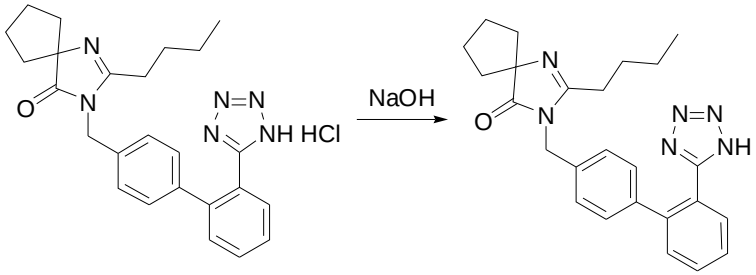


Fig 3.2.S.3.2-10 MS spectra of impurities obtained with IRB02

2.1.4 Potential Impurities in IRB03

The synthesis scheme for IRB02 and IRB03 is listed below:

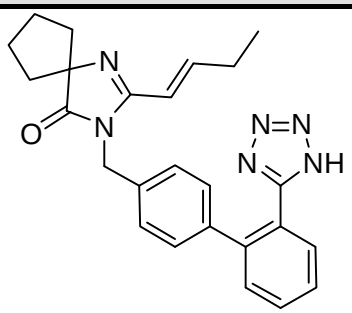
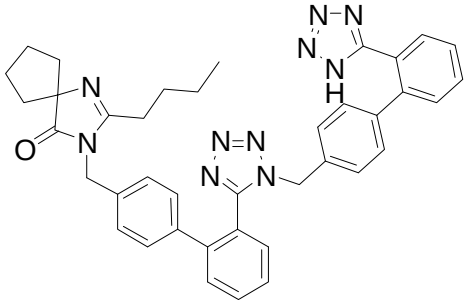
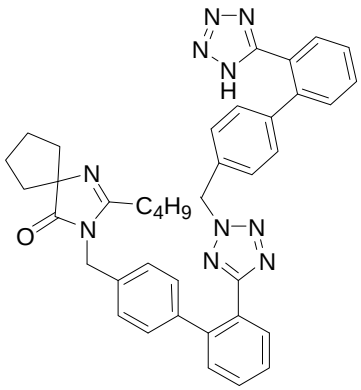


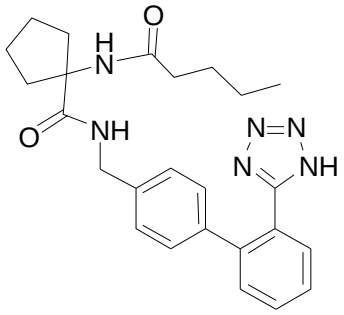
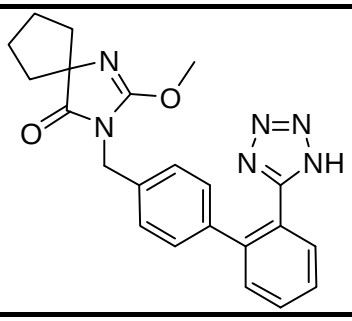
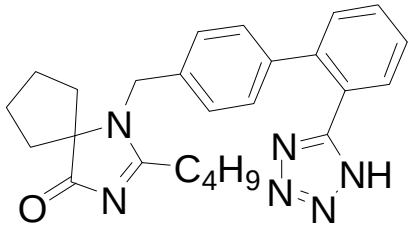
IRB02 **IRB03**

Potential process impurities in IRB03

The name, structure and source of the potential impurities in starting material of IRB03 are listed in the table below.

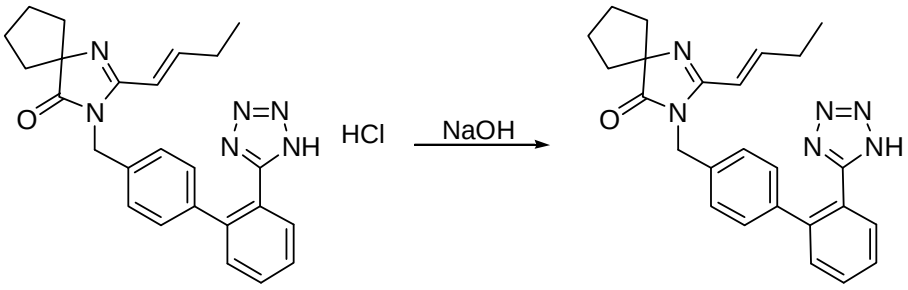
Table 3.2.S.3.2-10 Potential Impurities in IRB03

Impurity code	Structure	Source
Impurity 1		Side reaction
Impurity 2	 Or: 	Side reaction

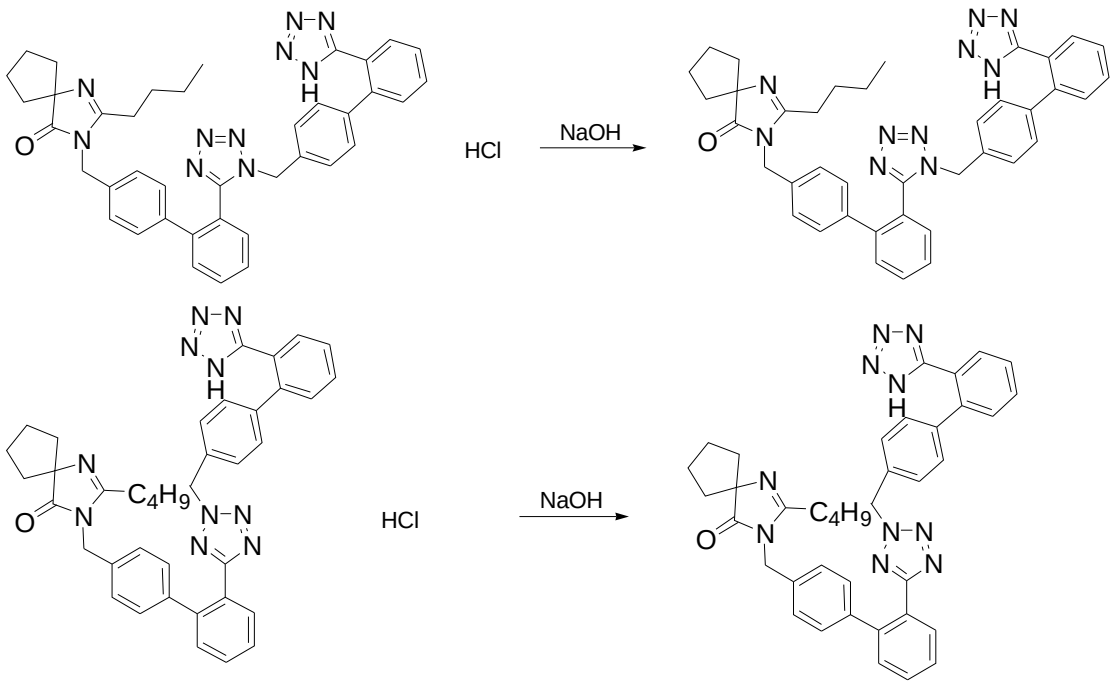
Impurity code	Structure	Source
Impurity A		Side reaction
Impurity 3		Side reaction
Impurity 3-9		Side reaction

Elaboration of potential impurities source in IRB03

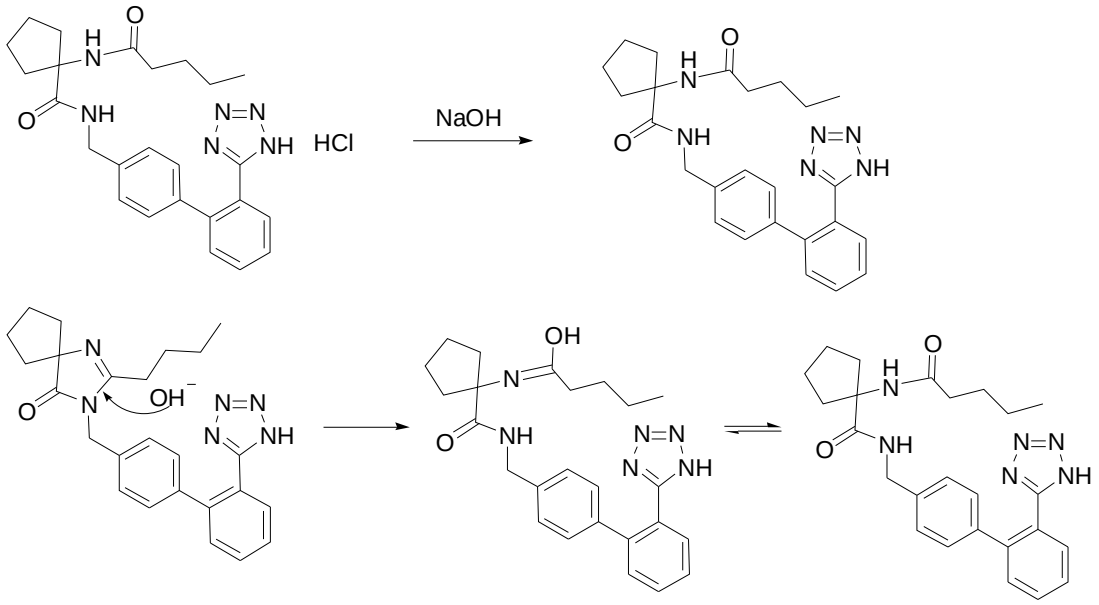
Impurity 1: Derivation from impurity 2-3



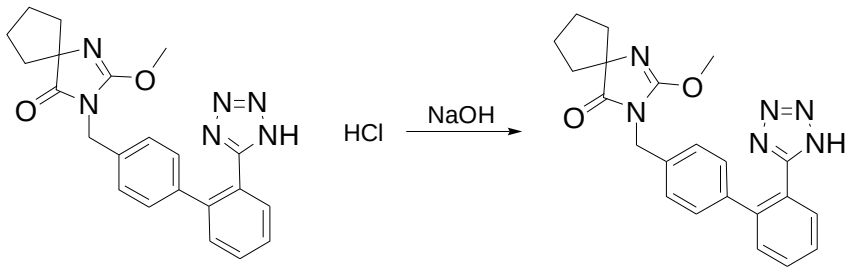
Impurity 2: Derivation from impurity 2-11



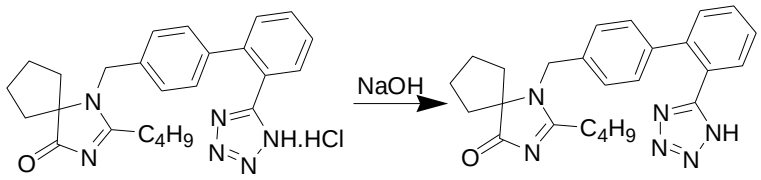
Impurity A: Derivation from impurity 2-4, and side reaction of IRB03 in present of sodium hydroxide.



Impurity 3: Derivation from impurity 2-5



Impurity 3-9: Derivation from impurity 2-9



Justification of the potential impurities in IRB03

The impurities in IRB03 are generated the impurities from IRB02. There are few impurities in IRB02, and the impurities generated in IRB03 will be much less. All these impurities can well dissolve in ethanol, and can be removed in the purification of IRB03 using ethanol, and further eliminated in the purification process of product with ethanol.

As impurities 1, 2 and 3 can dissolve in ethanol as well as impurity 3-9, the contents of these three impurities are controlled to be not more than 0.10% in IRB03 which further ensures the contents of these three impurities are in safe level even they carry over into the final product.

The test results listed below will indicate impurities 1, 2 and 3 are under 0.10% in IRB03, which further demonstrate the above discussion.

Table 3.2.S.3.2-11 Test Result of impurities in IRB03

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%

Conclusion

There are 5 potential impurities that may exist in IRB03 all are generated from impurities in IRB02. Their precursors haven been mostly removed from IRB02, and they will be much less in IRB03. The test results also demonstrate all impurities existing in IRB03 will not affect the quality of product.

The representative HPLC chromatograms of IRB03 is presented in the following page.

Fig 3.2.S.3.2-11 HPLC chromatogram obtained with IRB03

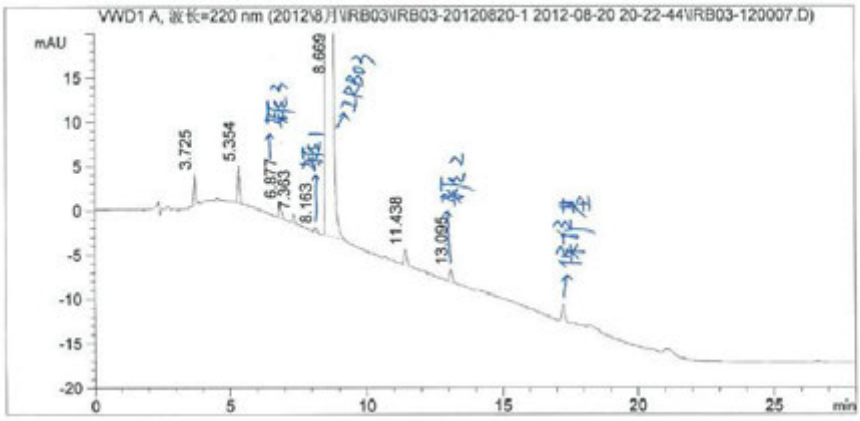
数据文件： D:\CHEM32\1\DATA\2012\8月\IRB03\IRB03-20120820-1 2012-08-20 20-22-44\IRB03-120007.D

检品信息： IRB03-120007

单批信息： IRB03-120007

报告模板类型： HEC-HPLC-JY0501-性能报告

仪器名称：	Agilent1200-液相色谱仪		
仪器编号：	JY0501	进样量：	5.00 ul
进样日期：	2012-8-20	进样次数：	1次
进样时间：	21:41:09	进样位置：	样品瓶 2
操作者：	YY		
采集方法：	D:\Chem32\1\DATA\2012\8月\IRB03\IRB03-20120820-1 2012-08-20 20-22-44\IRB03.M		
分析方法：	D:\CHEM32\1\METHODS\IRB03.M		



信号相关：

信号： VWD1 A, 波长=220 nm

保留时间 min	峰高 mAU	峰面积 mAU*s	塔板数	分离度	拖尾因子	对称因子	峰面积/%
3.725	3.48	17.81945	13411		1.506	0.824	0.1008
5.354	4.22	23.74552	21283	11.81	1.008	0.906	0.1343
6.877	1.69	10.51115	28514	9.81	0.890	0.894	0.0595
7.363	1.01	6.18683	34410	3.02	0.895	0.831	0.0350
8.163	0.49	3.11609	36403	4.84	0.874	0.750	0.0176
8.669	2522.69	17592.36133	36518	2.86	1.030	0.981	99.5266
11.438	1.73	12.31308	62152	15.15	0.900	0.884	0.0697
13.095	1.37	9.99450	74604	8.82	0.888	0.881	0.0565

检验人： 杨勇 2012.08.21 复核人： 2012.08.4

仪器编号： JY0501 Page 1 of 1

Fig 3.2.S.3.2-11 HPLC chromatogram obtained with IRB03

2.1.5 Potential impurities after purification

Intermediate IRB03 is crystallized in ethanol to provide IRB04. IRB04 is subsequently dried to provide IRB05 which is final product. Most of the process impurities can be dissolved in ethanol and removed in this step. The impurities before and after purification are tested and presented in the table below:

Table 3.2.S.3.2-12 Impurities in IRB03 and IRB05

	IRB-1208001		**IRB-1208002**		**IRB-1208003**	
	IRB03-120006	**IRB05-120006**	**IRB03-120007**	**IRB05-120007**	**IRB03-120008**	**IRB05-120008**
Impurity 1	0.02%	0.018%	0.02%	0.008%	0.02%	ND
Impurity 2	0.05%	ND	0.06%	ND	0.05%	ND
Impurity 3	0.06%	ND	0.06%	ND	0.06%	ND
Impurity A	ND	ND	ND	ND	ND	ND
Irbesartan	99.6%	99.9%	99.5%	99.9%	99.6%	99.9%

The results showed that most of the impurities can be removed by the purification process.

The limits of impurity A, unknown impurity and total impurities have been defined in the specification of final product. The detail data found in three submission batches are listed in the Table 3.2.S.3.2-3 under this section, which demonstrates the quality of product meets the Ph. Eur. requirements.

The representative chromatogram of impurities in IRB03 and IRB05 are presented in the following pages.

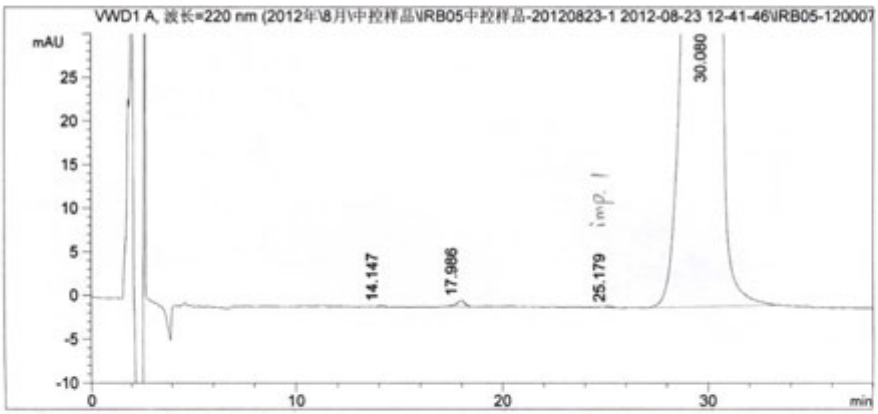
Fig 3.2.S.3.2 -12 Chromatogram obtained with IRB05

数据文件： D:\CHEM32\1\DATA\2012年\8月\中控样品\IRB05中控样品-20120823-1 2012-08-23 12-41-46\IRB05-120007.D
检品信息： IRB05-120007

单针信息： IRB05-120007

报告模板类型： HEC-HPLC-JY0500-性能报告

仪器名称：	Agilent1200-液相色谱仪		
仪器编号：	JY0500	进样量：	10.00 ul
进样日期：	2012-8-23	进样次数：	1次
进样时间：	13:21:51	进样位置：	样品瓶 22
操作者：	ZHW		
采集方法：	D:\Chem32\1\DATA\2012年\8月\中控样品\IRB05中控样品-20120823-1 2012-08-23 12-41-46\IRB有关物质.M		
分析方法：	d:\Chem32\1\METHODS\IRB有关物质.M		



信号相关：

信号： VWD1 A, 波长=220 nm

保留时间 min	峰高 mAU	峰面积 mAU*s	塔板数	分离度	拖尾因子	对称因子	峰面积/%
14.147	0.13	2.48980	11142		0.821	1.154	0.0068
17.986	0.68	19.23740	10782	6.24	0.790	1.279	0.0528
25.179	0.12	3.25342	14617	9.41	0.854	0.910	0.0089
30.080	695.48	36414.44531	9716	4.77	0.723	1.717	99.9314

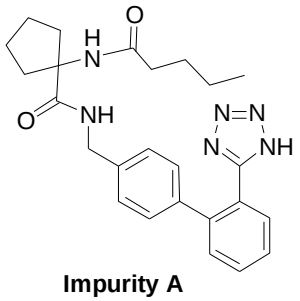
仪器编号： JY0500 Page 1 of 1

Fig 3.2.S.3.2 -12 Chromatogram obtained with IRB05

2.2 Degradation Products

2.2.1 Potential Degradation Impurity in Irbesartan

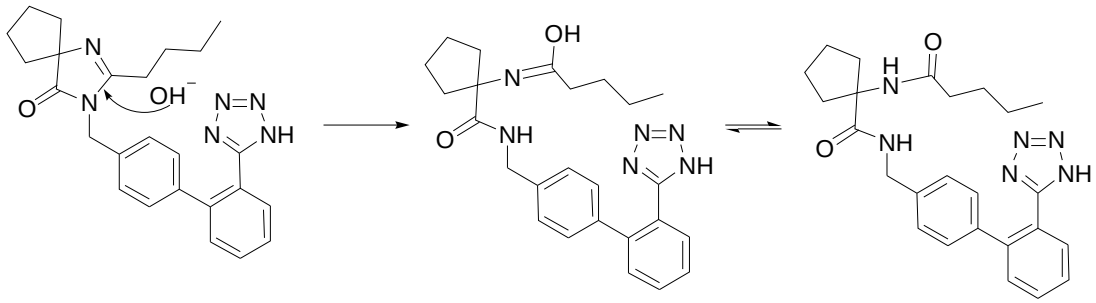
There is one possible degradation impurity in Irbesartan drug substance which is also a process impurity with a structure as below:



Impurity A

2.2.2 Degradation paths

Impurity A is generated from Irbesartan under alkaline condition, and the chemical mechanism is presented below:



Irbesartan **Impurity A**

2.2.3 Justification

Impurity A from degradation may generate in step III when sodium hydroxide is used. However it can well dissolve in ethanol and can be removed by purification process. And the limit of impurity A is specified in the specification of the final product based on the Ph.Eur. Irbesartan monograph.

2.2.4 Stability Test Results of Submission Batches

The accelerated stability and long-term stability data with related to related substances from three submission batches are summarized in Tables 3.2.S.3.2- 13 to 14.

Table 3.2.S.3.2-13 Accelerated stability data at from 0 month to 3 month

Batch Number	Impurity A		Any other impurity		Total impurities	
	0 month	3 month	0 month	3 month	0 month	3 month
IRB-1208001	ND	ND	0.06%	0.05%	0.06%	0.05%
IRB-1208002	ND	ND	0.06%	0.05%	0.06%	0.05%
IRB-1208003	ND	ND	0.06%	0.06%	0.06%	0.06%
Acceptance criteria	≤ 0.15%		≤ 0.10%		≤ 0.2%	

Table 3.2.S.3.2-14 Long-term stability Data at 3 months

Batch Number	Impurity A		Any other impurity		Total impurities	
	0 month	3 month	0 month	3 month	0 month	3 month
IRB-1208001	ND	ND	0.06%	0.05%	0.06%	0.05%
IRB-1208002	ND	ND	0.06%	0.05%	0.06%	0.05%
IRB-1208003	ND	ND	0.06%	0.06%	0.06%	0.06%
Acceptance criteria	≤ 0.15%		≤ 0.10%		≤ 0.2%	

2.2.5 Conclusion

The stability test results from 3 months of accelerated stability and long-term stability are well within the acceptance criteria and no obvious degradation occurs. The product of Irbesartan manufactured in Changjian Pharm. is relative stable.

2.3 Residual Organic Reagents

Impurity B: azide

Sodium azide used in the synthesis of starting material: BBTT. It is not used in the manufacturing process of Irbesartan. Azide cannot react directly with Irbesartan or its intermediate. Azide can well dissolve in water and can be removed step by step, and it is tested by HPLC. The detail procedure is described in *3.2.S.4.2 Analytical Procedures* of the application dossier. The test results in three submission batches are listed in table below.

Table 3.2.S.3.2-15 Test Results of Impurity B in Irbesartan Drug Substance

Test	Acceptance criterion	Batch Number		
		IRB-1208001	IRB-1208002	IRB-1208003
Impurity B	≤ 10 ppm	ND*	ND	ND
Batch size		75.6kg	75.2kg	76.8kg
Manufacturing date		20, Aug. 2012	22, Aug. 2012	24, Aug. 2012

* ND: below the DL (detection limit of Impurity B is 0.40ppm)

Results show that Imprurity B in product is below 10ppm in compliant to the criteria in Ph. Eur. monograph of Irbesartan.

2.4 Discuss briefly about the suitability of the monograph to control the potential impurities present in the substance

Impurity A is not found in the final product and the stability test. It is identified by USP Irbesartan Related Compound A RS. It could be detected using the monograph method. Refer to *3.2.S.4.3* Validation of HPLC Method for Determination of Related Substances.
Impurity B is not found in the final product and it will not increase during the stability test. It is identified by sodium azide. It could be detected using monograph method. Refer to *3.2.S.4.3* Validation of the Ion Chromatograph Method for the Impurity B.
It can be concluded that the Ph. Eur. Monograph 04/2010:2465 for Irbesartan is suitable to control the potential impurities in the substance.

3.2.S.3.2.3 Inorganic Impurities

Inorganic impurities are controlled through detection of heavy metals. The test procedure is described in *3.2.S.4.2 Analytical Procedures* of the application dossier. The test results in three submission batches are listed in table below. The detailed information about the batches in described in Section *3.2.S.4.4 Batch Analysis* of this dossier.

Table 3.2.S.3.2-16 Test Result of Inorganic Impurities in the Representative Batches

Tests	Acceptance Criteria	Batch Number		
		IRB-1208001	IRB-1208002	IRB-1208003
Heavy Metals	≤ 0.002%	Conforms	Conforms	Conforms
Batch Size (kg)		75.6	75.2	76.8
Manufacturing Date		20, Aug. 2012	22, Aug. 2012	24, Aug. 2012

The test results show that inorganic impurities in the representative batches comply with the acceptance criteria.

3.2.S.3.2.4 Residual Solvents

Only solvents of ethanol and toluene are used in the manufacturing of Irbesartan. And considering benzene may arise from toluene, it is also tested for the existence in the finished product. Concentration limits recommended in *ICH Q3C Impurities: Guideline for Residual Solvents* and In-house limit are presented in the table below for these three

solvents.

Table 3.2.S.3.2-17 Solvents Used in the Manufacture of Irbesartan

Solvent	Class	Usage	In-house Limit	ICH Q3C Limit	Test Method
Ethanol	Class 3	Purification solvent	5000 ppm	5000ppm	Quantitation Test
Toluene	Class 2	1. Reaction solvent in Step I . purification solvent in step II	890 ppm	890ppm	Quantitation Test
Benzene	Class 1	N/A	2 ppm	2 ppm	Quantitation Test

The levels of residual for ethanol, toluene and benzene are tested by GC method. The GC method is established with reference to *Ph.Eur.5.4* and *Ph.Eur.2.4.24.* The detailed analytical procedure is presented in *3.2.S.4.2 Analytical Procedures.* It was validated for accuracy and reliability under practical conditions and the data are presented in *3.2.S.4.3 Validation of Analytical Process.* Test results for residual solvents in three submission batches are listed in the following table.

Table 3.2.S.3.2-18 Residual Solvents in Three Submission Batches of Irbesartan

Test	Acceptance Criteria	Batch Number		
		IRB-1208001	IRB-1208002	IRB-1208003
Ethanol	≤ 5000 ppm	39 ppm	3088 ppm	586 ppm
Toluene	≤ 890 ppm	ND*	ND	ND
benzene	≤ 2 ppm	ND	ND	ND
Batch Size (kg)		75.6	75.2	76.8
Manufacturing Date		20, Aug. 2012	22, Aug. 2012	24, Aug. 2012

* ND: Not Detected (The detection limit of toluene is 6 ppm, and that of toluene is 0.6072 ppm)

The test results in the three submission batches are well within the acceptance criteria.We confirm that the residual solvents in Irbesartan manufactured by Changjiang Pharm comply with the requirements of *ICH Q3C Impurities: Guideline for Residual Solvents.*

The Residual Solvents Declaration is presented below.

Fig 3.2.S.3.2-13 Residual Solvents Declaration for Irbesartan Drug Substance

Yichang Changjiang Pharmaceutical Co., Ltd
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Email: xuelian1980@yeah.net Postal code: 443300

20 August 2012

RESIDUAL SOLVENTS DECLARATION

The solvents used in the manufacturing process of **Irbesartan** and their control levels are presented in **Table 01.**

Table 01

Class 1		
Name	Level	Method used
Benzene	Not more than 2ppm	In-house GC Method
Class 2		
Name	Level	Method used
Toluene	Not more than 890ppm	In-house GC Method
Class 3		
Name	Level	Method used
Ethanol	Not more than 5000ppm	In-house GC Method

We declare that the residual solvents in **Irbesartan** manufactured by Yichang Changjiang Pharmaceutical Co., Ltd complies with the requirements of ICH Q3C *Impurities: Guideline for Residual Solvents* and controlled in accordance with CPMP/QWP/450/03.

Zhu Qiaohong
Vice General Manager
Yichang Changjiang Pharmaceutical Co., Ltd

Fig 3.2.S.3.2-13 Residual Solvents Declaration for Irbesartan Drug Substance

3.2.S.3.2.5 Discussion on Impurities with Potential Genotoxicity

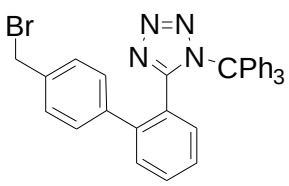
The potential genotoxicity of impurities presented in Irbesartan drug substance, including organic impurities, inorganic impurities and residual solvents are discussed below.

1. Organic Impurities

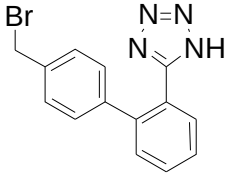
1.1 Related Substances

1.1.1 Potential Impurities

According to the guideline of Genotoxic Impurities (EMEA/CHMP/QWP/ 251344/2006), there may be two potential genotoxic impurities in Irbesartan. The information of potential genotoxic impurities is listed as below.



BBTT



Deprotect BBTT

Referring to EMEA CHMP guideline on the Limits of Genotoxic Impurities (EMEA/CHMP/ QWP/251344/2006), the concentration limits in ppm of potential genotoxic impurities in Irbesartan can be calculated using equation:

$$\text{Concentration limit (ppm)} = \frac{\text{TTC [µg/day]}}{\text{Dose[g/day]}} = \frac{1.5\text{µg/day}}{0.3\ \text{g/day}} = 5\ \text{ppm}$$

The determination of potential genotoxic impurities is carried out by an in-house HPLC method which has been validated to be suitable for its intended use. The test results of these impurities in three submission batches are listed below.

Table 3.2.S.3.2-19 Potential Genotoxic Impurities Observed in Three Submission Batches

Impurity	LOD of the method	Test result		
		IRB-1208001	IRB-1208002	IRB-1208003
BBTT	1 ppm	ND	ND	ND
Deprotected BBTT	1 ppm	3.6 ppm	2.8 ppm	3.7 ppm

The results show BBTT is undetected and deprotected BBTT is lower than 5ppm in our final product. So, these two impurities should not therefore cause any appreciable risk of genotoxicity.

1.1.2 Other impurities

Impurity A, its structure and limit are given in Ph.Eur. Irbesartan, and the results in three submission batches listed in Table 3.2.S.3.1-10 are well within the acceptance criteria. It should not therefore cause an appreciable risk of genotoxicity.

The other impurities, the possible structures of these impurities are analyzed in *Section 3.2.S.3.2.2 Organic Impurities* according to the reaction mechanism and LC-MS results. All the possible structure is similar to the structure of Irbesartan and there is no structure alert which shows any risk of genotoxicity. Furthermore, there is no any literature or evidence shows these possible structures have any known human relevant risks. The limit of these impurities is set to be not more than 0.10% according to the Ph.Eur. monograph and results showed with three submission batches are well within the acceptance criteria. So, all these impurities should not therefore cause any appreciable risk of genotoxicity.

1.2 Residual Organic Reagents

Impurity B is a potential genotoxic and its limit has been defined in Ph. Eur. monograph of Irbesartan with not more than 10 ppm.

Impurity B cannot react directly with Irbesartan or its intermediate, and it can well dissolve in water and can be removed step by step.

The limit of Impurity B in the product is tested by HPLC. The limits of Impurity B in three submission batches are listed in Table 3.2.S.3.2-15 which showed Impurity B cannot be detected in our product when detection limit is 0.40 ppm. It means the Impurity B in our product is far less than 10 ppm which is safe for human health.

2. Inorganic Impurities

There is no metal catalyst used in the manufacture of Irbesartan.

And the inorganic materials used in the manufacture of Irbesartan can be eliminated step by step, as water is used in purification process of step II and step III. The heavy metals test results in three submission batches are listed in Table 3.2.S.3.2-16 under this section, which complies with the limit prescribed in Ph. Eur. monograph of Irbesartan. The inorganic impurities should not therefore cause an appreciable risk of genotoxicity.

3. Residual Solvents

The solvents ethanol and toluene are used in the manufacturing process of Irbesartan.

Their residues in the final product are quite low, as they can be removed through several phase separations or centrifugations or recrystallization.

The test results in three submission batches are listed in Table 3.2.S.3.2-18 under this section, which show that residual toluene is not detectable in three submission batches. The content of ethanol is less than 5000ppm which is defined in ICH Q3C and Ph.Eur.5.4 and Ph.Eur.2.4.24. Therefore, the residual ethanol and toluene should not cause appreciable risk of genotoxicity.

Residual Benzene

Toluene is used in the manufacturing process for Irbesartan and therefore it is possible that benzene exists in the final product. The residues of benzene in three submission batches of Irbesartan have been tested according to the analytical procedure described in *3.2.S.4.2*. The validation of the procedure is provided in *3.2.S.4.3.* The limit of benzene is established to be 2ppm according to ICH Q3C *Impurities: Guideline for Residual Solvents*. The results are listed in 3.2.S.3.2-15, which show that residual benzene is not detectable in three submission batches of Irbesartan and therefore present no appreciable risk of genotoxicity.

4. Conclusion

The results described above can demonstrate that there is no risk of genotoxicity in Irbesartan manufactured at Yichang Changjiang Pharm.

3.2.S.3.2.6 Materials of Human or Animal Origin

The materials used in the manufacturing process of Irbesartan are not of human or animal origin and do not contain any genetically modified organism or generated from genetically modified organism.

The declarations are presented in the following pages.

Fig 3.2.S.3.2-14 TSE/BSE Declaration of Irbesartan drug substance

Fig 3.2.S.3.2-15 Letter of Declaration of Manufacture Regarding the Use of Material Containing Genetically Modified Organism

Yichang Changjiang Pharmaceutical Co., Ltd
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Email: xuelian1980@yeah.net Postal code: 443300

HEC

20 August 2012

TSE/BSE DECLARATION

We, **Yichang Changjiang Pharmaceutical Co., Ltd**, No.38-62, Binjiang Road, Yidu, Hubei Province, P.R.China, hereby confirm that materials used in the manufacturing process of **Irbesartan** are not of human or animal origin.

Zhu Qiaohong
Vice General Manager
Yichang Changjiang Pharmaceutical Co., Ltd

Fig 3.2.S.3.2-14 TSE/BSE Declaration of Irbesartan drug substance

Yichang Changjiang Pharmaceutical Co., Ltd
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HEC

20 August 2012

LETTER OF DECLARATION OF MANUFACTURE REGARDING THE USE OF MATERIAL CONTAINING GENETICALLY MODIFIED ORGANISM

We, **Yichang Changjiang Pharmaceutical Co., Ltd,** No.38-62, Binjiang Road, Yidu, Hubei Province, P.R.China, hereby declare that the materials used in the manufacturing process of **Irbesartan** do not contain any Genetically Modified Organism or generated from Genetically Modified Organism during production.

Zhu Qiaohong
Vice General Manager
Yichang Changjiang Pharmaceutical Co., Ltd

Fig 3.2.S.3.2-15 Letter of Declaration of Manufacture Regarding the Use of Material Containing Genetically Modified Organism