EPA Change Request for Approval for New Intermediate Process (T2633) and Change to Existing Process for Darunavir Ethanolate

1.0 Background

Janssen were granted approval by the EPA for the manufacture for a new intermediate process (T2633) for the completion of a Demonstration and 3 Validation Batches for the modified Darunavir Ethanolate (R319064) process (modified from 2nd Gen to 3rd Gen) – Reference LR026030, 15th Dec 2016.
Janssen now seek approval for production of the new intermediate process, T2633, as part of the commercial production of the 3rd Generation of Darunavir Ethanolate (R319064).

2.0 New Intermediate Step T2633

2.1 Overview of T2633

The following are charged to the reactor: Water, Sodium Carbonate, THF, T2660 and N-acetyl Sulfaniyl Chloride and stirred until the reaction is complete. The reaction mixture is allowed to settle and the aqueous layer is then removed. Hydrochloric Acid is then added. At this point carbon dioxide and isobutene are released. Water is then added and Sodium Hydroxide is dosed until a neutral pH is achieved. T2633 seed is charged and the material is crystallized. The product is centrifuged, the M/L is removed and the cake is washed with Water. The product is then isolated, discharged and subsequently dried. This is now the starting material of the RR391064 step. The total time to manufacture this step is 68 hours.

2.2 Raw Materials

The following are the confirmed list of raw materials and their quantities used for one step of T2633 production:

Solvents	Vol	Units	CAS#
Water	3595	L	N/A
Sodium Carbonate	51	KG	497-19-8
THF	559	L	109-99-9
T2660	269	KG	160232-08-6
N-acetyl Sulfaniyl Chloride	190	KG	121-60-8
Methanol	1278	L	67-56-1
Sodium Hydroxide (30%)	720	L	1310-73-2
Hydrochloric Acid	639	L	7647-01-0

Ethanol	320	L	64-17-5
T2633	2.7	KG	169280-56-2
Toluene	1500	L	108-88-3
Methansulfonic Acid	55	KG	-
Sodium Hydroxide (25%)	100	L	1310-73-2
Total	22909		

The above materials are included in the annual groundwater monitoring in accordance with Schedule 4 (ii) Groundwater monitoring, where applicable.

2.3 Waste

The following wastes will be generated:

- There is a phase split to remove the aqueous layer. This will be a volume of approx. 1000 L.
- The THF is distilled. This will be a volume of approx. 2000L.
- Carbon dioxide and isobutene are off-gases will be sparged to a reactor which will contain Toluene/Methansulfonic Acid (MSA) to remove the isobutene (See Section 2.4 below). The Toluene/MSA mixture, is neutralized with Sodium Hydroxide and sent to waste. This volume sent to waste is approx. 2000L (including the additional volume of the isobutene now in liquid form).

The total sent to waste is 5000L/batch. This represents 32% of the batch is sent to waste. This is not a significant amount of waste but the site will endeavor to reduce waste quantities where possible.

2.4 Emissions to Atmosphere

Isobutene is produced as an off-gas from the reaction for T2633. The existing site VOC Carbon Adsorption System (the VARA) will not effectively treat isobutene gas. The carbon will adsorb the isobutene, however it will flash off during the steam regeneration step due to low boiling point (-6.9 °C). Upgrades to the VARA will not be effective in treating isobutene. Hence it is proposed to continue using the scrubbing solution of Toluene/MSA to remove the isobutene before being sent to the VARA (existing emission point F1-1).

The basis for the Toluene/MSA scrubbing design was the article published in Organic Process Research & Development entitled "Minimizing Isobutylene Emissions from Large Scale tert-Butoxycarbonyl Deprotections" by Dias et al, based on experimental work completed in the Process Safety and Reaction Engineering Laboratory, Pfizer Global Research and Development (Ref. Attachment 1). This demonstrated that in laboratory experiments, in which the reactor off-gas was simply bubbled into a scrubbing bottle containing the toluene/MSA mixture, 99.6% of the isobutene could be removed. The experiments were repeated in a pilot plant scrubber of 25 cm diameter, in which an approximately 97% scrubbing efficiency was obtained. The somewhat poorer results in the pilot scale being attributed to possibly poorer mixing of the relatively immiscible toluene and MSA acid within the pilot plant scrubber system.

During the trial batches of Darunavir Ethanolate (RR319064) already completed in 2017, the Toluene/MSA scrubbing was employed to reduce the levels of isobutene. The following outlines both the theoretical quantities and the actual measured quantities based on the 2017 demonstration/validation batches.

2.4.1 Theoretical Quantities

T3622 + HCl -> T2633 + Isobutene (1m eq.) + CO_2 (1m eq.)

268.8Kg T2660 per batch / 336.48 (MW) → 799 mol per batch.

→ 799 mol x 1 mol eq. x 22.4 L = 17897 L CO_2 + **<u>17897 L isobutene</u>**

→ Total Gas evolved (CO_2 + Isobutene) 35795 L = 35.795 m3

However, for the third-generation process of Darunavir (R319064), the BOC deprotection of T003622 to T002633 was investigated (this work is fully detailed in the report 'Study in the RC1 reaction calorimeter: Scotten-Bauman coupling to T003622 and BOC deprotection to T002633' reference EDEB/161027, report number 0505 (Ref Attachment 2)) and demonstrated that the reaction mixture itself acts as a scrubber and only 10% of the isobutene evolved is released to the Toluene/MSA scrubber, that is, **<u>1789.7 L.</u>**

Therefore the isobutene quantity released to the Toluene/MSA Scrubber equates to **1789.7 L or 4.482Kg** (799 mol x 10% = 79.9 mol x 56.106 (atomic weight) = 4482.869 g = 4.482 Kg).

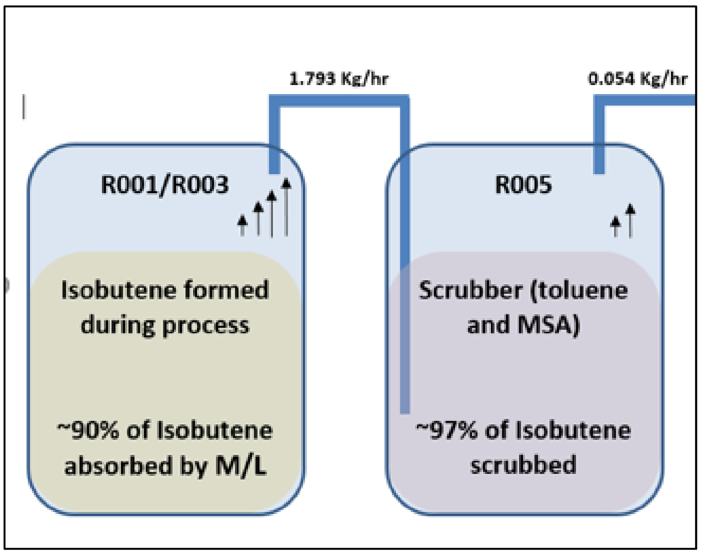
Since the dosing vessel is fitted with an orifice plate which restricts the flow of HCl into the reactor the dosing will take a minimum of 2.5hrs. Taking this flow as the worst case then 4.482 Kg of isobutene gas will be evolved over a 2.5 hrs period or **1.793 Kg/hr**.

(Please note the information detailed in the response to the EPA's request for additional information, Ref correspondence RI006713, dated 14th Dec 2016, incorrectly stated that the mass flow of Isobutene into the

scrubber would be 420kg/hr. This was due to incorrect interpretation of data available which has now been clarified as outlined above).

This **1.793 Kg/hr** isobutene is then passed through a scrubbing mixture of Toluene/MSA. Based on a scrubber efficiency of circa 97%[2] this equates to **0.134 Kg/2.5hrs** or **0.054 Kg/hr** isobutene being released to the site VARA**.** A schematic representation of the mass flow to/from the scrubber is presented below.

Figure 1 Isobutene scrubbing schematic



2.4.2 Measured Quantities

During the manufacturing T2633 for the Demo/Validation batches in 2017, online FTIR analysis was carried out on the outlet of the scrubbing vessel. The results from the FTIR analysis are summarized in Table 1. As can be seen from Table 1 the scrubber was effective in removing the isobutene to acceptable levels, achieving an average 99.12% removal of isobutene.

Additionally, during the T2633 manufacture there were no excursions in the TOC levels from the VARA, as presented in Attachment 3 and previously submitted to the EPA.

Table 1 – Scrubber Efficiency based on FTIR data (Demo/Validation Batches 2017)

Step	Date of Manufacture	Mass Flowrate of Isobutene in Vent Header (R005) (kg/hr)* (based on Max 30 Min Mean Conc and vent flowrate)	Theoretical Mass Flowrate of Isobutene Pre-Scrubber (kg/hr)	Mass flowrate of Isobutene Scrubbed from Vent Header (kg/hr)	% Efficiency of Scrubber (= Mass Flowrate of Scrubbed Isobutene/Theoretical Mass Flowrate of Isobutene x 100%)
Sequence 1	10-11th of May 2017	0.023227	1.793	1.770	98.70%
Sequence 2	N/A	N/A	N/A	N/A	N/A
Sequence 3	24-25th of May 2017	0.001966	1.793	1.791	99.89%
Sequence 4	04-05th of October 2017	N/A	N/A	N/A	N/A
Sequence 5	07-08th of October 2017	N/A	N/A	N/A	N/A
Sequence 6	10th of October 2017	N/A	N/A	N/A	N/A
Sequence 7	12-13th of October 2017	0.010827	1.793	1.782	99.39%
Sequence 8	17th of October 2017	0.023866	1.793	1.769	98.67%
Sequence 9	20th of October 2017	N/A	N/A	N/A	N/A
Sequence 10	22-23rd of October 2017	0.018817	1.793	1.774	98.95%
Sequence 11	25th of October 2017	N/A	N/A	N/A	N/A

N/A – Batch did not progress to the Isobutene release step or equipment set-up issues resulted in the FTIR not recording data.

2.4.3 Isobutene/Scrubbing in a Regulatory Context

Putting the Toluene/MSA scrubbing in a regulatory context, the following points can be noted: –

- such a system fits the criteria of process integration and reduction at source as advocated by the June 2016 BREF and associated 'BAT conclusions'.
- It also reduces the carry-over of isobutene, an extremely flammable gas, into the main plant vent header system, which from a process safety perspective is highly advantageous in terms of risk reduction
- Absorption, i.e. scrubbing, is a well-recognized abatement technique in all BAT related guidance.
- The removal efficiency of a scrubbing system is high, as has been demonstrated already in practical trials. It is worth noting that quantities of isobutene released to the scrubber during a full scale production batch will remain the exact same as for one of the validation batches.

2.5 Conclusion on New Intermediate Step T2633

While this is a new step being conducted on site, it will not have any significant impact on the existing licence conditions as follows:

- The new process is within the confines of the existing licence.
- There is no requirement for a new emission point. Preliminary abatement will remove isobutene before being sent to the existing VARA and Licensed emission point F1-1.
- Isobutene is covered by TA Luft Organics classification (Class II at the most).
- The employment of the preliminary abatement means the existing emission limit values in the Licence can be comfortably achieved.
- Monitoring of Organic emission levels can remain as per existing licence – Continuous TOC monitoring and monthly monitoring for TA Luft Classes.

3.0 2nd Generation to 3rd Generation

3.1 Current 2nd Gen Darunavir Ethanolate (Crude – RR319064) Process

3.1.1 Overview

Acetonitrile, DSC, T2675/Acetonitrile and Pyridine are charged and reacted together. When this is complete, T2633 and TEA are then charged to the reactor to complete an additional reaction step. Methylamine is then added to quench the reaction. Acetonitrile is removed by distillation and MTBE is added. Sodium carbonate solution is then added to remove impurities. The reaction mixture is allowed to settle and the aqueous layer is separated and sent to a waste tank. Sulphuric Acid is then added to remove the Pryridine and again the aqueous layer is separated. MTBE is then added to separate out the remaining aqueous layer. A second portion of Sodium Carbonate is added and the aqueous layer is separated. The Sodium Carbonate also neutralizes any traces of acid in the waste. Water is then used to remove any remaining sodium carbonate and the aqueous layer is removed. Acetonitrile and MTBE are then distilled and Ethanol is added. The reactor contents are cooled to crystallize the RR319064. The product is centrifuged, the M/L is removed and the cake is washed with Ethanol. The product is then isolated and discharged for further processing.

Processing of the current batch is approx. 61.5 hours.

3.1.2 Raw Materials

The following is the list of raw materials used in the current Darunavir Ethanolate (Crude – RR319064) process.

Codes	Solvents	Vol	Units	CAS#
84	Acetone (Bulk)	200	L	67-64-1
84	Acetone (Bulk)	400	L	67-64-1
497852	Acetonitrile (Bulk)	845	L	75-05-8
495011	DSC (DiSuccinimidyl Carbonate)	403.4	KG	74124-79-1
116407	T 2675 in Acetonitrile	195.2	KG	156928-09-5
117967	Pyridine	360.1	KG	110-86-1
497852	Acetonitrile (Bulk)	99	L	75-05-8
22398	Water (PFCS)	1191	L	N/A
6638	Sodium Carbonate	126.9	KG	497-19-8

497854	Sulphuric Acid	163.5	L	7664-93-9
6962	Sodium Sulphate	125.1	KG	7757-82-6
497921	T2633	575.6	KG	206361-99-1
8866	Triethylamine	133	KG	121-44-8
8866	Triethylamine	56	KG	121-44-8
497852	Acetonitrile (Bulk)	99	L	75-05-8
117966	Methylamine Sol. (41%)	46.3	KG	74-89-5
497853	Tert-Butyl methyl ether	880	L	1634-04-4
	Sodium Carbonate Sol.	816	Kg	497-19-8
497853	Tert-Butyl methyl ether	880	L	1634-04-4
	Sodium Carbonate Sol.	500	Kg	497-19-8
22398	Water (PFCS)	503	L	N/A
22398	Water (PFCS)	526	L	N/A
497851/ 89954	Ethanol Low Bioburden/ Ethanol denatured with MEK	1205	L	64-17-5/ 78-93-3
497851/ 89954	Ethanol Low Bioburden/ Ethanol denatured with MEK	723	L	64-17-5/ 78-93-3
613	Ammonia	225	L	N/A
	Total	11277.1	L	

3.1.3 Wastes

There is a total of 11,277 L of material used per batch.

As part of the process there is approx. 4,665 L of waste generated from the phase splits and treatment of these waste layers.

This means 41% of a batch is sent to waste.

3.2 3rd Generation Darunavir Ethanolate (Crude – RR319064) process:

3.2.1 Overview

T2633 and T2632 are charged to the reactor in Ethanol and refluxed. The next step of the process is similar to the final steps of the current Darunavir Ethanolate Process. The material is cooled to crystalize the RR319064. The product is centrifuged, the M/L is removed and the cake is washed with Ethanol. The product is then isolated and discharged for further processing.

The total time to manufacture this step is 17 hours.

3.2.2 Raw Materials

The following is the list of raw materials used in the current Darunavir Ethanolate (Crude – RR319064) process.

Codes	Solvents	Vol	Units	CAS#
	T2633	795.9	L	169280-56-2
	T2632	529.3	Kg	253265-97-3
	Ethanol Low Bioburden/ Ethanol denatured with MEK	5082	Kg	64-17-5/ 78-93-3
	Total	6407	L	

3.2.3 Waste

The 3rd Generation process is a much more simplified RR319064 step with no waste generated (only M/L and Washes from Centrifuge). There are no phase splits or waste treatment associated with this step.

3.3 Conclusion - 2nd Generation to 3rd Generation Darunavir Ethanolate

As can be seen from above the 3rd generation Darunavir Ethanolate is a far more efficient and environmentally beneficial over the lifecycle of the product as it requires less raw materials, takes less time to produce reducing energy costs and generates significantly less waste.

Attachment 3 TOC Levels from the VARA, F1.1., during T2633 batches in 2017

Date	24Hr max 30min Average	24Hr min 30min Average	24hr Average of 30min Averages	
03 January 2017	5.6	1.1	1.8	**50% Scale Development Start Date**
04 January 2017	2.1	1.0	1.4	
05 January 2017	2.2	0.6	1.4	
06 January 2017	2.2	1.0	1.5	
07 January 2017	2.8	1.0	1.6	
08 January 2017	2.8	1.0	1.7	
09 January 2017	3.1	1.0	1.6	
10 January 2017	3.8	1.0	1.9	
09 May 2017	3.9	1.7	2.6	**Demo/Validation Batches**
10 May 2017	4.1	2.0	3.1	
11 May 2017	8.2	2.4	4.0	
12 May 2017	9.6	2.9	4.7	
13 May 2017	7.2	2.5	4.0	
14 May 2017	5.7	2.5	3.8	
15 May 2017	2.9	2.0	2.4	
16 May 2017	4.5	2.2	2.9	
17 May 2017	7.6	0.0	1.9	
18 May 2017	8.4	0.0	2.0	
19 May 2017	18.1	0.0	7.4	*TOC Analyser could not be calibrated Flame Error. Reported to EPA.*
20 May 2017	1.2	0.0	0.4	
21 May 2017	1.5	0.0	0.7	
22 May 2017	3.2	0.0	0.9	
23 May 2017	5.5	0.0	1.1	
24 May 2017	5.9	0.0	1.1	*New TOC Analyser Fitted and Calibrated.*
25 May 2017	7.2	0.0	2.2	
26 May 2017	11.6	2.0	3.4	
27 May 2017	11.4	2.1	4.4	
28 May 2017	12.7	1.6	3.2	
29 May 2017	7.1	1.5	2.8	
30 May 2017	11.0	1.7	3.1	
31 May 2017	6.6	1.1	2.2	
26 Sep 2017	2.4	0.0	0.4	**Validation Batches Contd.**
27 Sep 2017	20.5	0.0	1.3	
28 Sep 2017	11.3	0.0	0.8	
29 Sep 2017	14.4	0.0	2.4	
30 Sep 2017	14.1	0.0	1.4	
01 October 2017	5.7	0.0	0.7	

02 October 2017	12.2	0.0	2.0
03 October 2017	21.7	0.4	3.4
04 October 2017	10.9	0.6	2.9
05 October 2017	11.2	1.0	3.7
06 October 2017	21.6	1.1	3.3
07 October 2017	11.9	1.0	3.2
08 October 2017	4.6	1.0	1.8
09 October 2017	8.8	1.0	2.8
10 October 2017	10.4	1.0	3.0
11 October 2017	13.4	1.0	2.8
12 October 2017	12.4	1.0	2.1
13 October 2017	3.7	1.2	1.7
14 October 2017	3.2	1.0	1.4
15 October 2017	2.0	1.0	1.3
16 October 2017	2.0	1.0	1.2
17 October 2017	8.9	1.0	2.4
18 October 2017	7.6	0.5	1.5
19 October 2017	4.2	0.5	0.8
20 October 2017	5.4	0.4	1.0
21 October 2017	3.0	0.5	0.8
22 October 2017	3.0	0.5	0.8
23 October 2017	5.9	0.5	1.2
24 October 2017	5.1	0.5	1.1
25 October 2017	6.2	0.5	1.2
26 October 2017	5.0	0.2	1.7