PRESENT MANUFACTURING PROCESS DA	**PROPOSED MANUFACTURING PROCESS** A
Section II.B.2	**Module 3.2.P.3.3**
The method of manufacture of Actigrip Gola involves a series of mixing, solubilisation and dissolution steps.	The method of manufacture of Actigrip Gola involves a series of mixing, solubilisation and dissolution steps.
Two manufacturing processes are employed: - continuous process (principal process) - batch process (secondary process) Both processes utilise the same method of preparing the concentrate. The processes differ in the means by which the final dilution is performed.	Two manufacturing processes are employed: - continuous process (principal process) - batch process (alternative process)
Manufacture of the concentrate The flavours and the active are dissolved in ethanol. Polysorbate 60, previously molten, is added and dissolved in the alcholic phase. Some of the purified water is added. The water-soluble ingredients are dissolved in the mixture and the remaining part of water is added to form the concentrate.	
Continuous process The manufacture is divided into 2 steps. - manufacture of a concentrate (x10). The concentrate contains all the ingredients except the	Continuous process The manufacture is divided into 2 steps. - manufacture of a concentrate. The concentrate contains all the ingredients except the total quantity of

total quantity of water. - dilution of the concentrate with purified water. Via a volumetric pump the concentrate and the purified water are simultaneously injected into a static mixer. From the concentrate, several batches of final product are produced and one batch of finished product is defined by one day's production.	water. - dilution of the concentrate with purified water. Concentrate and the purified water are simultaneously injected via a volumetric pump into a static mixer. **One batch of concentrate corresponds to one batch of bulk finished product.**
Batch process The concentrate is dispersed in half the quantity of water. The remaining quantity of water is added and stirred until homogeneous.	Batch process **All the ingredients** are dispersed in about half the quantity of water. The remaining quantity of water is added and stirred until homogeneous
Continuous process	Continuous process
The mouthwash is prepared by initially forming the concentrate, which is then diluted in a ratio of concentrate: purified water, 1:9 (volume/volume).	The mouthwash is prepared to be initially forming the concentrate, which is then diluted. **The manufacturing process is described below, for 10,000 litres of concentrate which will provide 67,390 litres of finished product**.
Equipment - 10,000 litre manufacturing tank equipped with a propeller - 2,200 litre intermediate manufacturing tank - two 2000 litre buffer tanks - static mixer - in line spectrophotometer - dosing pump - ~~3~~ filter cartridges (0.2 µm)	Equipment - manufacturing tank equipped with a propeller - intermediate manufacturing tank - **storage** tank - static mixer - in line spectrophotometer or flow meter - dosing pump - filter cartridges (**0.45 and** 0.22 µm)
Example for a 10,000 litre concentrate corresponding to 100,000 litre of finished product	
Step 1 Weigh into a 10,000 litre stainless steel manufacturing tank, equipped with a propeller stirrer: purified water 3,440.567 kg ethanol (96%) 3,597.000 kg	Step 1 Incorporate purified water in the manufacturing tank.

	Step 2 **Incorporate and dissolve EDTA-Ca** **IPC1 : Control of dissolution**
Step 2 Incorporate in the intermediate tank: ethanol (96%) 369.667 kg levomenthol 18.600 kg peppermint oil 64.000 kg anise oil 39.250 kg methyl salicylate 18.600 kg eucalyptus oil 1.100 kg clove oil 8.450 kg	Step 3 Incorporate in the intermediate tank: ethanol 96% levomenthol eucalyptus oil **IPC2: Control of dissolution**

polysorbate 60 (molten) 700.000 kg hexetidine 100.000 kg Rinse hexetidine container with ethanol (96%) 33.333 kg. ethanol (96%) for rinsing 333.333 kg After stirring: visual control	Step 4 Incorporate and mix in the intermediate tank: **ethanol 96%** polysorbate 60 (molten) hexetidine Rinse container with ethanol 96% IPC3: Control of dissolution Step 5 Rinse the intermediate tank with ethanol 96%
Step 3 Whilst stirring add: saccharin sodium 22.000 kg citric acid monohydrate 41.800 kg azorubine 2.300 kg Stir for 30 min.	Step 6 Incorporate in the manufacturing tank: saccharin sodium citric acid monohydrate Step 7 Incorporate in the manufacturing tank: azorubin 85%
	Step 8 **Incorporate and mix in the intermediate tank:** **purified water** **sodium hydroxide**
	Step 9 **Transfer the solution of sodium hydroxide prepared in step 8, into the manufacturing tank, qs pH 5.5 ± 0.2.**
Step 4 Rinse the intermediate tank with purified water 500.000 kg Transfer into the 10,000 litre manufacturing tank and stir for 30 minutes. IPC1: Analytical control of the concentrate (including pH measurement).	Step 10 Rinse the intermediate tank with purified water. Step 11 Mix the solution. IPC4: pH measurement
	Step 12 **Filter the solution using 0.45 µm membrane cartridges.** **Store the solution before dilution and filling in bottles.**
Step 5 Continuous dilution in a ratio of concentrate: purified water 1:9 v/v with a volumetric dosing pump and a static mixer. Purified water 89,810.000 kg. IPC2: Continuous control of dilution	Step 13 Dilute the concentrate with purified water, with a volumetric dosing pump and static mixer. IPC5: continuous control of dilution
Step 6 Buffer storage	
Step 7	Filter the solution using 0.22 µm membrane cartridges.

In line filtration with 0.2 µm membrane cartridges. IPC3: Control of filters	
Step 8 Packaging. IPC4: Analytical control IPC5: Filling volume IPC6: Packaging compliance	Step 14 Filling and Packaging **IPC6: Density** IPC7: Average fill volume IPC8: Packaging compliance
Section II.D.1	Module 3.2.P.3.4
Specifications of the concentrate	Specifications of the concentrate
Description: A clear, red liquid	Description: A clear, red liquid **with a mint odour**
Weight per ml at 20°C: 0.910 to 0.948 g/ml	Weight per ml at 20°C: **0.955 to 0.975 g/ml**
pH at 20°C (1/10 dilution): 4.7 – 5.1	pH at 20°C (after dilution): **5.5 ± 0.2**
Ethanol content: 49.0 to 54.2 % (v/v)	Ethanol content: **33.0 to 36.5** % (v/v)
Control methods	Analytical methods
pH at 20°C … Dilute 5.0 ml of concentrate in 50 ml of water (R) …	pH at 20°C … Dilute **7.5** ml of concentrate in 50 ml of water (R) …
Azorubin identification by TLC ….. Test Solution (extraction of the azorubin from concentrate) Dilute 5.0 ml of concentrate with water and complete to 50.0 ml with the same solvent. …..	Azorubin identification by TLC ….. Test Solution (extraction of the azorubin from concentrate) Dilute 7.5 ml of concentrate with water and complete to 50.0 ml with the same solvent. …..
Identification and assay of ethanol by GC … Test Solution Weigh accurately 5 ml of concentrate in a 50 ml volumetric flask and make up to volume with demineralised water. Introduce 10.0 ml of this solution into a 50 ml volumetric flask and make up to volume with solution B. ….	Identification and assay of ethanol by GC … Test Solution Weigh accurately **7.5** ml of concentrate in a 50 ml volumetric flask and make up to volume with demineralised water. Introduce 10.0 ml of this solution into a 50 ml volumetric flask and make up to volume with solution B. ….
pH at 20°C (1/10 dilution): 4.7 – 5.1	pH at 20°C (after dilution): **5.5 ± 0.2**
Ethanol content: 49.0 to 54.2 % (v/v)	Ethanol content: **33.0 to 36.5** % (v/v)
Control methods	Analytical methods
pH at 20°C … Dilute 5.0 ml of concentrate in 50 ml of water (R) …	pH at 20°C … Dilute **7.5** ml of concentrate in 50 ml of water (R) …
Azorubin identification by TLC ….. Test Solution (extraction of the azorubin from concentrate) Dilute 5.0 ml of concentrate with water and complete to 50.0 ml with the same solvent. …..	Azorubin identification by TLC ….. Test Solution (extraction of the azorubin from concentrate) Dilute 7.5 ml of concentrate with water and complete to 50.0 ml with the same solvent. …..
Identification and assay of ethanol by GC …	Identification and assay of ethanol by GC …

Test Solution Weigh accurately 5 ml of concentrate in a 50 ml volumetric flask and make up to volume with demineralised water. Introduce 10.0 ml of this solution into a 50 ml volumetric flask and make up to volume with solution B. ….	Test Solution Weigh accurately **7.5** ml of concentrate in a 50 ml volumetric flask and make up to volume with demineralised water. Introduce 10.0 ml of this solution into a 50 ml volumetric flask and make up to volume with solution B. ….
Identification and assay of hexetidine by HPLC … Sample solution Into a 50 ml volumetric flask weigh accurately 5 ml of concentrate and complete to volume with water R. Dilute 10.0 ml of the s to 50.0 ml with ethanol R.	Identification and assay of hexetidine by HPLC … Sample solution Into a 50.0 ml volumetric flask weigh accurately **7.5** ml of concentrate and complete to volume with water. Into a 50.0 ml volumetric flask introduce 10.0 ml of this solution. Complete to volume with ethanol **and mix with a magnetic stirrer to homogenize the solution.** **Sample solutions must be prepared and directly placed in vials in the autosampler (to protect against light and temperature variation).** **Sample solutions are stable for 20 hours in the autosampler at 25°C.**
Section II.B.2	Module 3.2.P.3.3
Batch process	Batch process
The concentrate is dispersed in half the quantity of water. The remaining quantity of water is added and stirred until homogeneous.	**All the ingredients** are dispersed in half the quantity of water. The remaining quantity of water is added and stirred until homogeneous.
Equipment - 1,000 litre manufacturing tank equipped with a propeller - 10,000 litre manufacturing tank equipped with a propeller - centrifugal pump - filter cartridges (0.22 µm)	Equipment - intermediate manufacturing tank - manufacturing tank equipped with a propeller - centrifugal pump - filter cartridges (0.22 µm)
Example for a 1,000 litre concentrate	
	Step 1 Incorporate purified water in the main tank
	Step 2 **In an intermediate tank, incorporate purified water.** **Incorporate and dissolve EDTA-Ca.** **Transfer into the main tank.** **IPC1: Control of dissolution**
Step 1 The raw materials are weighed into a 1,000 litre stainless steel manufacturing tank, equipped with a propeller stirrer: ethanol (96%) 430.333 kg Whilst stirring add: levomenthol 1.860 kg peppermint oil 6.400 kg anise oil 3.925 kg	Step 3 The raw materials are weighed into the intermediate tank, equipped with a propeller stirrer: ethanol 96% Whilst stirring, add: levomenthol

methyl salicylate 1.860 kg eucalyptus oil 0.110 kg clove oil 0.845 kg hexetidine 10.000 kg Rinse hexetidine container with ethanol (96 %) 2.500 kg Add polysorbate 60 (molten) 70.000 kg After stirring: visual control. No droplet detected	eucalyptus oil hexetidine Rinse hexetidine container with ethanol 96% polysorbate 60 (molten) purified water saccharin sodium citric acid monohydrate
	Step 4 **In a drum, incorporate and mix:** **purified water** azorubin **purified water** **Transfer to the intermediate tank**
Step 2 Whilst stirring add: purified water 394.057 kg saccharin sodium 2.200 kg citric acid monohydrate 4.180 kg azorubine 0.230 kg Stir for 30 min.	Step 5 Stir **until complete dissolution and transfer to the manufacturing tank.** **IPC2: Control of dissolution**
	Step 6 **Incorporate and mix in the intermediate tank:** **Purified water** **Sodium hydroxide** Step 7 **Transfer the solution of sodium hydroxide prepared in step 6, into the manufacturing tank, qs pH 5.5 ± 0.2.**
Step 3 Storage of the concentrate	
Step 4 In a 10,000 litre tank add purified water 4,490.500 kg Add the concentrate stored in step 3.	
Add the remaining water rinsing the pipes at the same time: purified water 4,490.500 kg	Step 8 Rinse the intermediary tank with purified water and transfer to the manufacturing tank. Step 9 **Mix.** Step 10 **Complete to final volume, with purified water**. Step 11

IPC1: pH may be adjusted at this stage	**Mix.** IPC3: pH measurement
Step 5 In line filtration with 0.2 µm membrane cartridges. IPC2: Control of filters	Step 12 Filter the solution using 0.22 µm membrane cartridges.
Step 6 Packaging. IPC3: Analytical control IPC4: Filling volume IPC5: Packaging compliance	Step 13 Fill and Pack. IPC4: **Density** IPC5: Average fill volume IPC6: Packaging compliance

variazione B.II.b.4 *z)* - Tipo IB unforeseen - modifica della dimensione e della formulazione del lotto*

MANUFACTURING FORMULA PRESENT **DA**			**MANUFACTURING FORMULA PROPOSED** **A**	
Section II.B.1			Module 3.2.P.3.2	
Manufacturing formula			Batch formula	
			The typical batch sizes for Actigrip Gola are: **67,390 litres for the continuous process** 10,000 litres for the batch process	
Manufacturing formula for continuous process			Manufacturing formula for continuous process	
Typical batch size: 100,000 litre or 60,000 litre. Each 10,000 litre of concentrate provides 100,000 litre of finished product, after dilution. Each 6,000 litre of concentrate provides 60,000 litre of finished product, after dilution.			The typical batch size for the concentrate is 10,000 litres which, after dilution, provides **67,390 litres of finished product.** **The ratio of dilution is 1 litre of concentrate for 6.739 litres of diluted finished product.**	
Ingredient	**10,000 l of concentrate**	**6,000 l of concentrate**	**Ingredient**	**10,000 l of concentrate**
Hexetidine	100.000 kg	60.000 kg	**Hexetidine**	**67.39 kg**
Polysorbate 60	700.000 kg	420.000 kg	**Polysorbate 60**	**471.73 kg**
Citric Acid Monohydrate (1)	41.800 kg	25.080 kg	**Citric Acid Monohydrate**	**28.17 kg**
Saccharin Sodium	22.000 kg	13.200 kg	**Saccharin Sodium**	**14.83 kg**
Azorubin (85%) (E122) (2)	2.300 kg	1.380 kg	**Azorubin (85%) (E122)** (1)	**1.55 kg**
~~**Methylsalicylate**~~	18.600 kg	11.160 kg	**---**	**---**
Levomenthol	18.600 kg	11.160 kg	**Levomenthol**	**47.17 kg**
~~**Peppermint Oil**~~	64.000 kg	38.400 kg	**---**	**---**
~~**Anise Oil**~~	39.250 kg	23.550 kg	**---**	**---**
Eucalyptus Oil	1.100 kg	0.660 kg	**Eucalyptus Oil**	**0.741 kg**
~~**Clove Oil**~~	8.450 kg	5.070 kg	**---**	**---**
---	---	---	Sodium Calcium	67.39 kg