Section A1 Applicant

Annex Point IIA1

1.1 Applicant

Name: PURAC Biochem
Address: Arkelsedijk 46
4206 AC Gorinchem
The Netherlands
Telephone: +31 (0) 183 695 695
Fax number: +31 (0) 183 695 602
E-mail address: t.van.dongen@purac.com

1.2 Manufacturer of Active Substance (if different)

Name: PURAC Biochem
Address: Arkelsedijk 46
4206 AC Gorinchem
The Netherlands
Telephone: +31 (0) 183 695 695
Fax number: +31 (0) 183 695 602
E-mail address: t.van.dongen@purac.com
Location of manufacturing plant: Gorinchem, the Netherlands

Name: PURAC bioquímica
Address: Gran Vial 19-25
08160 Montmeló (Barcelona)
Spain
Telephone: +34 93 568 6300
Fax number: +34 93 568 3955
E-mail address: t.van.dongen@purac.com
Location of manufacturing plant: Montmeló (Barcelona), Spain

Name: PURAC sínteses
Address: Av. Rui Barbosa, 521
Campos dos Goytacazes – RJ
CEP 28015-520
Brazil
Telephone: +55 22 2737 7200
Fax number: +55 22 2737 7210
E-mail address: t.van.dongen@purac.com
Location of manufacturing plant: Campos dos Goytacazes, Brasil

Section A1 Applicant

Annex Point IIA1

Name: PURAC America
Address: 650 Industrial Park Road
Blair, Nebraska 68008
USA
Telephone: +1 402 533 1800
Fax number: +1 402 533 1801
E-mail address: t.van.dongen@purac.com
Location of manufacturing plant: Blair, Nebraska, USA

Name: PURAC Thailand
Address: 485/10 RMS Building, 4th Floor
Sukhumvit Road
Tambol Huay Pong
Amphoe Muang
Rayong 21150
Thailand
Telephone: +66 (0) 38 683 440
Fax number: +66 (0) 38 683 443
E-mail address: t.van.dongen@purac.com
Location of manufacturing plant: Tambol Huay Pong, Amphoe Muang, Rayong, Thailand

1.3 Manufacturer of Product(s) (if different)

1) Product 1 PT2:

Name: [redacted]
Address: [redacted]
Telephone: [redacted]
Fax number: [redacted]
E-mail address: [redacted]

2) Product 2 PT3:

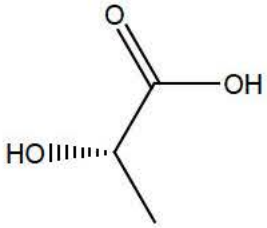
Name: [redacted]
Address: [redacted]

Section A1 Applicant

Annex Point IIA1

		[redacted]
	Telephone:	[redacted]
	Fax number:	[redacted]
	E-mail address:	[redacted]
3) Product 3	PT4:	
	Name:	[redacted]
	Address:	[redacted]
	Telephone:	[redacted]
	Fax number:	[redacted]
	E-mail address:	[redacted]
4) Product 4	PT6:	
	Name:	PURAC Biochem
	Address:	Arkelsedijk 46 4206 AC Gorinchem The Netherlands
	Telephone:	+31 (0) 183 695 695
	Fax number:	+31 (0) 183 695 602
	E-mail address:	t.van.dongen@purac.com

Section A2 Identity of Active Substance

Subsection (Annex Point)			Official use only
2.1	**Common name (IIA2.1)**	L(+) Lactic acid (See Document IVA2-02 and IVA2-03, included in the confidential part)	x
2.2	**Chemical name (IIA2.2)**	(S)-2-hydroxypropanoic acid	x
2.3	**Manufacturer´s development code number(s) (IIA2.3)**	PURAC SY-83 (See Document IVA2-01, included in the confidential part)	
2.4	**CAS No and EC numbers (IIA2.4)**		
2.4.1	**CAS-No**	79-33-4	
2.4.2	**EC-No**	201-196-2	
2.4.3	**Other**	Not applicable	
2.5	**Molecular and structural formula, molecular mass (IIA2.5)**		
2.5.1	**Molecular formula**	$C_3H_6O_3$	
2.5.2	**Structural formula**	 (S)-2-hydroxypropanoic acid	
2.5.3	**Molecular mass**	90.08 g/mol	
2.6	**Method of manufacture of the active substance (IIA2.1)**	See Document III_A 2.6 in the confidential part of the dossier.	x
2.7	**Specification of the purity of the active substance, as appropriate (IIA2.7)**	g/kg g/l % w/w % v/v L(+)-lactic acid: lower limit 92.95 mean 93.5 upper limit 94.04 Based on Doc IV, A2_02, as submitted on 14-02-2008	
2.8	**Identity of impurities and additives, as appropriate (IIA2.8)**	Impurities and identity of impurities are included as separate formats (A2.8) for each impurity in the confidential part.	
2.8.1	**Isomeric composition**	Stereochemical purity of lactic acid in the 93% aqueous solution: ≥99% L(+) lactic acid and < 1% D(-) lactic acid.	

Section A2 Identity of Active Substance

2.9	**The origin of the natural active substance or the precursor(s) of the active substance (IIA2.9)**	Metabolic substance in all living cells

Evaluation by Competent Authorities

Use separate "evaluation boxes" to provide transparency as to the comments and views submitted

EVALUATION BY RAPPORTEUR MEMBER STATE

Date 2015/10/23

Materials and methods

Conclusion

Reliability

Acceptability

Remarks The information on purity of L (+) Lactic acid given in this document is based on the initially submitted data from 2008. In order to make the whole dossier more comprehensible the corresponding information are kept in the documents. Due to the fact that with the BPR a five batch analysis is requested and L (+) Lactic is manufactured at 5 sites we requested the corresponding data from the applicant. For the results of the 5 batch analyses, which build the base of the final specification of L (+) Lactic acid, please refer to section 1.3 of the confidential Doc II A.

EVALUATION BY RAPPORTEUR MEMBER STATE

Date 2009/03/01

Materials and methods The correct quotation of the following filed entries is:

2.1 Common name : L(+) Lactic acid,

the additional details to Document IV are not necessary

2.2 Chemical name: (S)-2-Hydroxypropanoic acid (IUPAC)

Propanoic acid, 2-hydroxy-, (2S)- (CAS)

2.6 The existence of an equilibrium system is added in the confidential part A2.

Conclusion The revised version is included

Reliability 1

Acceptability acceptable

Remarks The information on impurities and additives given in this document are based on the initially submitted data from 2008. In order to make the whole dossier more comprehensible the corresponding information are kept in the documents. Due to the fact that with the BPR a five batch analysis is requested and L (+) Lactic is manufactured at 5 sites we requested the corresponding data from the applicant. For the results of the 5 batch analyses, which build the base of the final specification of L (+) Lactic acid, please refer to section 1.3 of the confidential Doc II A.

COMMENTS FROM ...

Date *Give date of comments submitted*

Results and discussion *Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.*
Discuss if deviating from view of rapporteur member state

Conclusion *Discuss if deviating from view of rapporteur member state*

Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	
Date	*Give date of comments submitted*
Results and discussion	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant´s summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A2.10

Annex Point IIA2.10

Exposure data in conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) amending Council Directive 67/548/EEC

Subsection		Official use only
2.10.1 Human exposure towards active substance	The human exposure during production and its use in biocides, is limited in relation to the human exposure by the total production and use of lactic acid (food, pharmaceutical, cosmetics, and feed).	
2.10.1.1 Production		
i) Description of process	The total production in or import into Europe of L(+) lactic acid in 2005 was in the range of 70.000 ton. The portion produced for biocides in 2005 was less than 1.5% of total production.	
ii) Workplace description iii) Inhalation exposure iv) Dermal exposure	The production of lactic acid in modern factories (PURAC factories are all certified for ISO 9001 and ISO 14001) is in closed installations and packed in containers by automatic filling equipment. Human exposure during production only possible when equipment is failing or by human failures. An estimation of 0.1% losses by failures/leakages, thus for biocide production a loss of 1000 kg. This estimation is based on industrial experience and the yields of the factories. Only a small part of that will be human exposure, as the spill will come on the ground mainly and maybe 100 kg lactic acid on the skin of the production personnel. This amount is spread over the year and over several persons working in 5 shifts in a continuous process. The operators are instructed to wear rubber gloves.(break through time > 8 hours); face-shield; long sleeved clothing, and chemical resistant apron boots.	
2.10.1.2 Intended use(s)		
1. Professional Users		
i) Description of application process ii) Workplace description iii) Inhalation exposure iv) Dermal exposure	L(+)lactic acid will be used in biocide product types 2 (private area & public health), 3 (veterinary hygiene), 4 (food and feed disinfectants) and 6 (in-can preservatives). For all these applications its use in 2005 was 1000 ton and it will grow to more than 2000 ton in 2008. These biocides will be used in cleaning and washing formulations on surfaces (toilet, bathrooms, and kitchen) and normally will not come in contact with humans. Also in the food and feed area it is used to disinfect the food processing areas, to clean the facilities, under normal use conditions it will not exposed to persons. In practice it can be estimated that some biocide formulation, not intended, can come in contact with human skin or by oral intake, maybe 1% of the formulation, thus 10-20 ton per year. Compared with the intended use of L(+)lactic acid in food and cosmetics in Europe this amount is not significant and not relevant.	
2. Non-professional Users including the general public		
(i) via inhalational contact (ii) via skin contact	L(+)lactic acid will be used in biocide product types 2 (private area & public health), 3 (veterinary hygiene), 4 (food and feed disinfectants) and 6 (in-can preservatives). For all these applications its use in 2005	

Section A2.10 Annex Point IIA2.10	Exposure data in conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) amending Council Directive 67/548/EEC	
(iii) via drinking water (iv) via food (v) indirect via environment	was 1000 ton and it will grow to more than 2000 ton in 2008. These biocides will be used in cleaning and washing formulations on surfaces (toilet, bathrooms, and kitchen) and normally will not come in contact with humans. Also in the food and feed area it is used to disinfect the food processing areas, to clean the facilities, under normal use conditions it will not exposed to persons. In practice it can be estimated that some biocide formulation, not intended, can come in contact with human skin or by oral intake, maybe 1% of the formulation, thus 10-20 ton per year. Compared with the intended use of L(+)lactic acid in food and cosmetics in Europe this amount is not significant and not relevant.	
2.10.2 Environmental exposure towards active substance	99% of the active substance in biocide formulations, after its use, will be found on surfaces and on the ground where it will be washed away with water. Thus practically all material will turn up in the drain and in via sewer-pipes come in wastewater treatment facilities of the cities. L(+)lactic acid is biodegradable and will be degraded to CO_2 and water in the sewer and wastewater treatment facility.	
2.10.2.1 Production		
(i) Releases into water (ii) Releases into air (iii) Waste disposal	During production a loss of 0.1% via leakages/spills is estimated based on a long experience with the production of lactic acid, thus 1-2 ton per year for the active substance. Practically all material will be washed away as it is very good water soluble and will turn up in the drain and sewer-pipes and finally be degraded in the waste water treatment facility of the factories of PURAC.	
2.10.2.2 Intended use(s)		
Affected compartment(s): water sediment air soil Predicted concentration in the affected compartment(s) water sediment air soil	99% of the active substance (1000 ton in 2005 and 2000 ton in 2008) will be found on surfaces and on the ground. After its use, the water soluble biocide will be flushed with water and will turn up in the drain and sewer-pipes of the municipality and the wastewater facility of the cities, where the biodegradable L(+)lactic acid is degraded into CO_2 and water.	x

Section A2.10
Annex Point IIA2.10

Exposure data in conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) amending Council Directive 67/548/EEC

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2009/04/27
Materials and methods	The applicant's statement regarding the emission to the environment from production of the a.s. is deemed to be plausible by RMS. During national authorisation of b.p. having lactic acid as a.s., the emission to the environment via formulation shall be considered. <u>General comments to chapter 2.10.2.2 Intended use(s)</u> Exposure data relevant for the life cycle stage "use" are missing. However, emission estimation for this life cycle stage is described by the applicant in Doc II-B, chapter 8.3. With respect to the different intended uses within the different PT's, the influence of emissions on the environmental compartments should be discussed more differentiated. The active substance (a.s.) is produced in the chemical industry within the EU. The exposure during the production of the a.s. is not assessed by the rapporteur under the requirements of the BPD. However, the rapporteur assumes that the production is performed in conformity with national and European occupational safety and health regulations.
Conclusion	Exposure data of the a.s. are sufficient with regard to the life cycle stages considered. More detailed information as well as missing information is given in Doc II-B, chapter 8.3.
Reliability	
Acceptability	acceptable
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Results and discussion	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table 1

Section A3 **Physical and Chemical Properties of Active Substance (LACTIC ACID 93% SOLUTION IN WATER)**

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
3.1 Melting point, boiling point, relative density (IIA3.1)								
3.1.1 Melting point	Not mentioned	Pure, crystalline solid lactic acid	53.0°C	The melting point of pure crystalline lactic acid was determined.	N		A3.1.1-01 Van Dongen (2006a)	3.1.1.a

Section A3 **Physical and Chemical Properties of Active Substance (LACTIC ACID 93% SOLUTION IN WATER)**

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
	Not mentioned	93%		Two situations are relevant 1. The eutectic composition of monomeric lactic acid and water is 62% lactic acid. The eutectic temperature is –27°C. This means that if crystallisation takes place of solutions with lactic acid concentrations higher than 62% w/w and at temperatures higher than –27°C, only pure lactic acid will crystallises. Below concentrations of 62% monomeric lactic acid and at temperatures above –27°C only water will crystallise. At temperatures below –27°C both lactic acid and water will crystallise separately. No 'freezing' of the mixture will occur.	N		A3.5-01 Van Dongen (2007a)	3.1.1.b

Section A3 Physical and Chemical Properties of Active Substance (LACTIC ACID 93% SOLUTION IN WATER)

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
				2. when a normal solution of around 90% lactic acid, i.e. a solution containing both monomeric lactic acid and lactic acid oligomers, is cooled, even down to –80°C no crystallisation occurs. The only thing that happens is an enormous increase in viscosity. This increase in viscosity prevents crystallization; this effect is related to glass transition (see references). When lactic acid crystals are added to an aqueous solution of around 90% w/w at equilibrium (i.e. with lactic acid oligomers), these crystals dissolve, even at 4°C (Personal Observations, G. Nanninga, PURAC).			A3.1.1-02	

Section A3 Physical and Chemical Properties of Active Substance (LACTIC ACID 93% SOLUTION IN WATER)

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
				The effect of increasing viscosity of highly concentrated solutions on the propensity of such solutions to stay supercooled instead of freezing or separating into their solid constituting components is a.o. supported by the work of Slama and Kodejs (1979). They conclude that if a solution has a viscosity at the liquidus temperature of ≥ 10 mPa.s, it can be supercooled. 93% lactic acid has a viscosity of 930 mPa.s at 0 °C, thus indicating that it is almost unavoidable that, with increasing viscosity at lowering the temperature, it will only stay supercooled, and will not solidify in any way.			A3.1.1_03 Slama and Kodejs (1979)	

Section A3 Physical and Chemical Properties of Active Substance (LACTIC ACID 93% SOLUTION IN WATER)

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
3.1.2 Boiling point	Not mentioned	88% 93%	**result:** 122 ° C **pressure:** 1.013 hPa **Not provided**	It is not possible to give one single boiling point for L(+) lactic acid. For the boiling points of aqueous solutions of lactic acid only approximate values can be given. An 88% solution, for instance, starts to boil at 122°C. After a few minutes the boiling temperature raises already to 130°C. There are two reasons why the boiling point of an 88% aqueous solution is not stable: - The composition of the oligomers in the solution changes and therefore the boiling point elevation. - The evaporation of a relatively small amount of water will change the concentration.	N		A3.1.2-01 Van Dongen (2006b)	3.1.2.a

Section A3 **Physical and Chemical Properties of Active Substance (LACTIC ACID 93% SOLUTION IN WATER)**

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
				The difference between 88% and 90% may be only 2% w/w. Expressed in molal concentrations (mol/kg water) it is however a difference between 81 and 100 mol/kg. (boiling point elevations are proportional with the molal concentration)				3.1.2.b
	Not mentioned	Pure lactic acid	**result:** >200 ° C **pressure:** 1.013 hPa	The boiling point of pure lactic acid is difficult to determine.	N		A3.1.2-01 Van Dongen (2006b)	
3.1.3 Bulk density/ relative density								

Section A3 **Physical and Chemical Properties of Active Substance (LACTIC ACID 93% SOLUTION IN WATER)**

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
Bulk/rel. density 1	Not mentioned	80.0% @ 25°C 88.6% @ 25°C 93.0% @ 25°C	1.1860 1.2006 1.2130	Holten (1971) gives at page 23 a table with densities of aqueous solutions of lactic acid at different temperatures and concentrations. These data were used for a regression of the density as function of temperature and concentration. The result for an aqueous solution of lactic acid with a concentration of 93% w/w at 20°C is a density of 1.213 g/cm3 at 20°C. z = a + bx + cy a = 1.020 b = 0.00222 c = -0.000695 in which: z = density g/cm3 x = concentration % w/w y = temperature °C	N		A3.1.3-01 Van Dongen (2006c)	3.1.3

Section A3 **Physical and Chemical Properties of Active Substance (LACTIC ACID 93% SOLUTION IN WATER)**

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
3.2 Vapour pressure (IIA3.2)	Joback method Modified Grain Method	100%	**temperature:** 20 °C **result:** 0.0041 mbar	The atmospheric boiling point of monomeric lactic acid cannot be determined experimentally. It can however be estimated. The Joback group contribution method (Joback K.G., Reid R.C., "Estimation of Pure-Component Properties from Group-Contributions", Chem.Eng.Commun., 57, 233-243, 1987) predicts a boiling point of 508 K for lactic acid, based on a boiling point of 453 K for 2-chloropropionic acid and group contributions of 38.13 K and 92.88 K for chlorine and hydroxyl groups respectively. Using an estimated enthalpy of vaporization of 40 kJ/mol, the Clausius-Clapeyron equation predicts a vapour pressure for the subcooled liquid at ambient pressure and temperature of 9.5e-4 atm. The modified Grain group contribution method predicts an ambient vapour pressure of 3.7e-5 atm.	N		A3.2-01 Van Dongen (2006d) A3.2.1-03	3.2.a

Section A3 **Physical and Chemical Properties of Active Substance (LACTIC ACID 93% SOLUTION IN WATER)**

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
	Calculation	93%	**6.701 mbar @ 20°C**	At room temperature pure monomeric lactic acid is a crystal. Its melting point is 53°C. While measuring the vapour pressure up to 53°C might give the vapour pressure of solid lactic acid, raising temperature above 53°C will initiate the stepwise polymerisation of lactic acid with the associated formation and evolution of water. When measuring the vapour pressure, you actually measure the vapour pressure of water under those conditions.			A3.2-02 Nanninga (2008)	3.2.b

Section A3 **Physical and Chemical Properties of Active Substance (LACTIC ACID 93% SOLUTION IN WATER)**

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
				For purposes of process design many in-house data were used to derive a reliable description of the vapour/liquid equilibrium (VLE) of lactic acid, its oligomers and water. This learns that an aqueous solution of 93% w/w of lactic acid at chemical equilibrium starts to boil at 132°C (partial vapour pressure of monomeric lactic acid: 11 mbar). At 20°C the partial vapour pressure of water of this solution is 6.7 mbar while the partial vapour pressure of monomeric lactic acid is < 0.004 mbar.				
3.2.1 Henry´s Law Constant (Pt. I-A3.2)	EPIWIN calculation	100%	**calculated: result: 1.13 E-7 atm-m^3/mole (bond contribution method) 3.39 E-9 atm-m3/mole (from estimated solubility and vapour pressure)**	Henry's law constant was estimated for pure L(+) lactic acid. Details in A3.2.1-03. For Pv/Saq method, Pv was 0.0286 mm Hg (estimated, modified Grain method) and Saq was 1E+006 mg/L (estimated: miscible).	N		A3.2.1-03 US-EPA (2008)	3.2.1

Section A3 **Physical and Chemical Properties of Active Substance (LACTIC ACID 93% SOLUTION IN WATER)**

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
3.3 Appearance (IIA3.3)								
3.3.1 Physical state	In-house method		Aqueous solution 88% (w/w)	Appearance of a 93% solution in indistinguishable from the appearance of an 88% solution.			A3.3-01	3.3.1
3.3.2 Colour	In-house method		≤ 100 Apha					3.3.2
3.3.3 Odour	In-house method		Not applicable					3.3.3
3.4 Absorption spectra (IIA3.4)								
UV/VIS		neat	UV/VIS spectra are included in Holten (1971). Maximum absorption is found at 210 nm				A3.4-02 Holten (1971b)	3.4.b UV

Section A3 **Physical and Chemical Properties of Active Substance (LACTIC ACID 93% SOLUTION IN WATER)**

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
		0.12%	Maximum absorption is found at 210 nm (water absorption	A3.4_02 contains a review of the UV absorption behaviour of lactic acid. This clearly shows that at wavelengths from 250 nm down to 210 nm, the absorbance of lactic acid steadily increases. Wavelengths <210 nm are irrelevant in nature; they are also irrelevant since at these wavelengths the absorbance of water will always dominate the UV absorption of aqueous solutions. A UV spectrum of a more dilute solution of lactic acid would therefore not be qualitatively different from the spectrum supplied in Document IV A3.4_04. Taken together, Documents IV A3.4_02 and _04 completely define the UV absorption behaviour of lactic acid in aqueous solution. The spectrum in Document IV A3.4-05 confirms this.			A3.4.-05 Lieuwen (2008)	3.4a UV

Section A3 **Physical and Chemical Properties of Active Substance (LACTIC ACID 93% SOLUTION IN WATER)**

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
IR			IR spectra are included in the expert statement	O-H (alcohol) stretching; 3600 cm^{-1} C-H stretching; 3000 cm^{-1} O-H (acid) stretching; 2900 cm^{-1} C=O stretching; 1800 cm^{-1}	N		A3.4-01 Van Dongen (2006f) A3.4-04 Van Dongen (2007)	3.4 IR
NMR			NMR spectra of crystalline and 90% lactic acid are included in Holten (1971).	Water as a solvent is incompatible with NMR spectroscopy. Therefore, it is not useful to try and take an NMR spectrum of 93% aqueous solution of lactic acid. This would, theoretically, yield a quantitative (i.e. all peaks directly proportional to the relative abundance of the oligomer) superposition of the NMR spectra of the individual monomer and oligomers present, on top of an 'absorption' band for water over the entire width of the spectrum. No interpretable details would remain in the resultant spectrum.			A3.4-03 Holten (1971c)	3.4 NMR

Section A3 **Physical and Chemical Properties of Active Substance (LACTIC ACID 93% SOLUTION IN WATER)**

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
MS			An MS spectrum for the pure compound is included in the expert statement		N		A3.4-01 Van Dongen (2006f)	3.4 MS
			A GC-MS run is included for the 93% solution	This gives a GC chromatogram for the two main components, viz lactic acid and lactoyllactic acid (the dimer). MS spectra for both components are included. The spectrum for lactic acid is identical to that of the pure substance, with no Mother ion and a dominating peak at m/z 45 containing 2 oxygens (COOH+). The spectrum for lactoyl lactic acid also shows no Mother ion. The first non-negligible peak is for the lactoyl moiety at m/z 89. Major peaks are COOH+ at m/z 45, and possibly $C_2H_2O_3$, at m/z 74.	N		A3.4.-05 Lieuwen (2008)	3.4 MS

Section A3 Physical and Chemical Properties of Active Substance (LACTIC ACID 93% SOLUTION IN WATER)

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
3.5 Solubility in water (IIA3.5)		100%	86.1% lactic acid at 20°C	At 20°C, the solubility of monomeric lactic acid in water is 86.1%; the total concentration of lactic acid then is in the range of 94%.	N		A3.5-01 Van Dongen (2007a)	3.5.a
		93%	miscible	A lactic acid solution of any concentration up to at least 100%, at chemical equilibrium is fully miscible with water. Lactic acid solutions of low concentration are concentrated by evaporation of water at elevated temperature and reduced pressure. During evaporation to any concentration up to 100% no phase separation, solid/liquid or liquid/liquid, occurs during either the concentration step itself, or at cooling to room temperature (or below) after having reached chemical equilibrium (see also 3.1.1).			A3.5-01 Van Dongen (2007a)	3.5.b
3.6 Dissociation constant (-)	Calculated		pKa=3.85		N		A3.6-01 Van Dongen (2007b)	3.6

Section A3 Physical and Chemical Properties of Active Substance (LACTIC ACID 93% SOLUTION IN WATER)

Subsection (Annex Point)		Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
3.7	**Solubility in organic solvents, including the effect of temperature on solubility (IIIA3.1)**	Methanol 2-ethylhexanol	Crystals Crystals	**result:** 78.6 % wt **temperature:** 20°C **result:** 29 % wt **temperature:** 20°C		N		A3.7-01 Van Dongen (2007a)	3.7
3.8	**Stability in organic solvents used in b.p. and identity of relevant breakdown products (IIIA3.2)**				Not required according to the Technical Notes for Guidance on Data requirements, as the products do not contain organic solvents.				

Section A3 **Physical and Chemical Properties of Active Substance (LACTIC ACID 93% SOLUTION IN WATER)**

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
3.9 Partition coefficient n-octanol/water (IIA3.6)	Shake-flask method.	Crystalline	**Log Kow = -.074**	Van Lieshout (1997) measured the partition of lactic acid over water and several alcohols. For monomeric lactic acid, degree of polymerisation 1, he found a value of Ko/w = 0.18 (logPo/w = -0.74) for the lowest concentration, Table 2a in the report. In a PURAC internal report (A3.9-06) the literature values of logPo/w are reviewed. What Van Lieshout found was confirmed in literature, logPo/w = -0.72. Van Lieshout also measured the partition of lactic acid containing lactoyllactic acid and higher oligomers. The higher the degree of polymerisation the higher the logP value. Very recently pure lactoyllactic acid was crystallised for the first time. The partition of lactoyllactic acid was determined; logPo/w = -0.32 (A3.9-04) Thereby the logP values of the tri, tetra and pentamers are also known. For each step in the oligomerisation logP will increase with 0.4 units.	N		A3.9-05 Van Lieshout (1997) A3.9-06 Nanninga (2003)	3.9a

Section A3 Physical and Chemical Properties of Active Substance (LACTIC ACID 93% SOLUTION IN WATER)

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
	Several methods.	93%	**result:** -0.6	The pH dependency of the octanol/water partition is given by the following relationships: logD = logP(o/w) – log(1 + 10(pH – pKa)) for acids and logD = logP(o/w) – log(1 + 10(pKa – pH)) for bases Lactoyllactic acid (HL2) has a slightly higher logP(o/w) value; –0.32 (PURAC in-house measured value). For every oligomerisation step, at least till the pentamer of lactic acid (HL5), logP(o/w) values increase with 0.4.	N		A3.9-01 Van Dongen (2007c) A3.9-04 Nanninga. (2008) A3.9-05 Van Lieshout (1997)	3.9b
3.10 Thermal stability, identity of relevant breakdown products (IIA3.7)		Lactic acid 80%	≥ 5 years when stored at ambient conditions				A3.10-01 Van Dongen (2007d)	3.10a
	In-house method, stability tested at 25 and 40°C up to 5 years	Lactic Acid 90 and 80%	Storage stability is ≥ 5 years at 25 and 40°C, for both concentrations		N	1	A3.10-03 Van Dongen (2007g)	3.10b

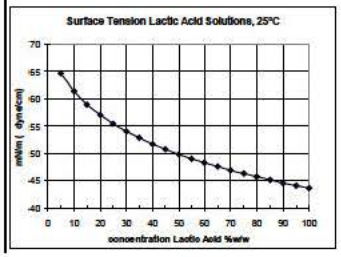
Section A3 Physical and Chemical Properties of Active Substance (LACTIC ACID 93% SOLUTION IN WATER)

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
3.11 Flammability, including auto-flammability and identity of combustion products (IIA3.8)			Not applicable, product is an aqueous solution	From the structural formula and composition of the substance it can be concluded that the substance does not evolve any flammable gases in contact with water or humid air and that the substance is stable at room temperature in air and is not pyrophoric. A solution of lactic acid is as combustible as a sucrose solution of the same strengths. The determination of the flash point of an aqueous solution of lactic acid (90%) failed. When heated to 130°C the vapour still could not be ignited. (ISL FP93 5G, closed cup) Since 93% lactic acid is an aqueous solution, and it can be shown that even at elevated temperatures, its vapour consist mainly of water, and it will not flash at temperatures at least as high as 130 °C, it is stated that 93% lactic acid will not auto-ignite.			A3.12-02 A3.2-02	

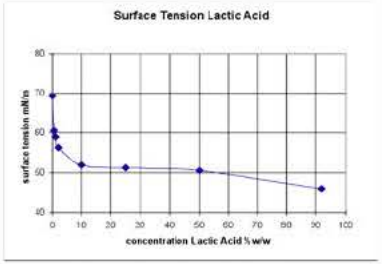
Section A3 Physical and Chemical Properties of Active Substance (LACTIC ACID 93% SOLUTION IN WATER)

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
	EC A.15 DIN 51794 IEC 79-4	92.8% solution in water	400°C at atmospheric pressure (1011.4 – 1018.9 hPa)	At this temperature, water is flash-evaporated, leaving finely divided lactic acid; the flammability and autoflammability of such a material is akin to a dust conflagration.	Y		A3.11-01 Baltussen (2009)	
3.12 Flash-point (IIA3.9)		88% solution in water	> 150°C	Holten page 38: Flash Point No exact determination of the flash point has been performed; it is, however, not less than 74°C, determined in closed cup for an acid of not less than 88% by weight. From A3.12-02:	N		A3.12-01 Holten (1971a)	
		pure		A final simple experiment in which a small cup, filled with lactic acid (100%), was put in silicone oil of 150°C, it was proven that the flashpoint lies above 150°C. It was not possible to put the lactic acid on fire.			A3.12-02	

Section A3 **Physical and Chemical Properties of Active Substance (LACTIC ACID 93% SOLUTION IN WATER)**

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
3.13 Surface tension (IIA3.10)		79% free acid	@ 25°C: 44.9 mN/m				A3.13-01 Van Dongen (2007e)	3.13
		1% solution	@ 25°C: 70.6 mN/m	The surface tension of lactic acid solutions of different concentrations has been measured at 25°C. Together with the surface tension of pure water (72) and the concentration dependency the result is shown in the graph below.  			A3.13-01 Van Dongen (2007e) A.3.1.2_03	3.13

Section A3 **Physical and Chemical Properties of Active Substance (LACTIC ACID 93% SOLUTION IN WATER)**

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
		1% solution	@ 25°C: 59.0 mN/m	The surface tension of lactic acid solutions of different concentrations has been measured at 25°C. The result is shown in the graph below.  Graph: Surface tension lactic acid solutions			A3.13-03 Van der Hoeven (2008a)	3.13
		0.92% solution (1% solution of 92% lactic acid in water, in water)	58.9 mN/m				A3.13-04 Van der Hoeven (2008b)	3.13

Section A3 Physical and Chemical Properties of Active Substance (LACTIC ACID 93% SOLUTION IN WATER)

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
		0.093% lactic acid in water (1 g/L active substance in water)	70.7 mN/m	Test was done according to OECD 115.			A3.13-05 Baltussen (2008)	3.13
3.14 Viscosity (-)		80% @ 25°C 88.6% @ 25°C	18.4 cP 36.9 cP				A3.14-01 Van Dongen (2007f)	
3.15 Explosive properties (IIA3.11)				From structural reasons and composition of the substance it can be concluded that the substance has no explosive properties.				
3.16 Oxidizing properties (IIA3.12)				From structural reasons and composition of the substance it can be concluded that the substance has no oxidizing properties.				
3.17 Reactivity towards container material (IIA3.13)			No reactivity was observed in the stability test.				A3.10-01 A3.10-2	

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2009/03/01
3.1.1 Melting point	3.1.1.a The correct quotation of the following field entries is: Purity: pure, crystalline solid lactic acid Results: 53 °C, pressure: not specified Reference: C.H. Holten, Lactic acid, Verlag Chemie, Weinheim, 1971, S. 22. The given remark is not necessary to be mentioned
Conclusion	
Reliability	2
Acceptability	acceptable
Remarks	
Date	2009/03/01
3.1.1 Melting point	3.1.1.b Purity: 93 % L-(+)-Lactic acid Results: no melting until – 80 °C Remarks: Expert statement
Conclusion	
Reliability	4
Acceptability	acceptable
Remarks	
Date	2009/03/01
3.1.2 Boiling point	3.1.2.a Remarks/Justification: It`s not possible to give a single boiling point for 93 % L-(+)-Lactic acid. The composition of the oligomers in the solution changes and therefore the boiling point elevates. The evaporation of small amounts of water changes the concentration, too. An initial boiling point of the aqueous solution of L-(+)-Lactic acid is affected by the heating rate and the amount of water evaporated before boiling. Therefore it`s not possible to determine this endpoint for the aqueous solution. The given value is not valid. Reference: Van Dongen (2006b)A3.1.2-01
Conclusion	Adopt applicant´s revised version
Reliability	4
Acceptability	acceptable
Remarks	

Date	2009/03/01
3.1.2 Boiling point	3.1.2.b
	The experimental determination of the boiling point is disturbed by polymerisation of L-(+)-Lactic acid with the associated formation and evolution of water, therefore the calculation of this endpoint is accepted.
	Method: EPIWIN v. 1.4.1 (adapted Stein and Brown Method)
	Purity: 100 % L-(+)-Lactic acid
	Results: 204.2 °C (calculated)
	Reference: Van Dongen (2006b) A3.1.2-01
Conclusion	Adopt applicant´s revised version
Reliability	2
Acceptability	acceptable
Remarks	

Date	2009/03/01
3.1.3 Bulk density/relative density	The correct quotation of the following field entries is:
	Purity: 93 % L-(+)-Lactic acid
	Results: 1.213 (T = 20 °C) (calculation from literature values)
	Densities of aqueous solutions of Lactic acid of various concentrations have been determined in literature. They vary almost linearily with concentration and temperature. The density of the 93 % L-(+)-Lactic acid is calculated using these results. The temperature was corrected to 20 °C according to the submitted values.
	Reference: C.H. Holten, Lactic acid, Verlag Chemie, Weinheim, 1971, S. 23-27.
Conclusion	Adopt applicant´s revised version
Reliability	2
Acceptability	acceptable
Remarks	

Date	2009/03/01
3.2 Vapour pressure	3.2.a
	The correct quotation of the following field entries is:
	Method: 92/69/EC, A.4 (Calculation, modified Grain Method)
	Purity: 100 % L-(+)-Lactic acid
	Results: 0.4 Pa (T = 20°C)
	Reference: G.P. v. Lieshout, EQUI2.BAS, May 1996
Conclusion	
Reliability	2
Acceptability	acceptable
Remarks	

Date	2009/03/01
3.2 Vapour pressure	3.2.b
	Due to the high water part, it is considered not to be scientific to determine or calculate the vapour pressure of a 93 % L-(+)-Lactic acid solution. The result of 670 Pa is only the partial vapour pressure of the water of the solution and it does not completely characterise the 93 % L-(+)-Lactic acid.
Conclusion	
Reliability	4
Acceptability	acceptable
Remarks	

Date	2009/03/01
3.2.1 Henry`s Law Constant	The Henry`s Law constant is not determinable for a 93 % aqueous solution of L-(+)-Lactic acid because of the existing equilibration system with oligomers and water.
	The determination of a Henry`s Law constant for L-(+)-Lactic acid is not scientific, because in water the equilibrium is immediately formed. The vapour pressure and water solubility is only based on calculation respectively estimation.
Conclusion	
Reliability	4
Acceptability	acceptable
Remarks	No further requirement.

Date	2009/03/01
3.3 Appearance	
3.3.1 Physical state	The correct quotation of the following field entries due to the safety data sheet is:
	Method: visual assessment
	Purity: 88 % L-(+)-Lactic acid
	Results: liquid (aqueous solution)
	GLP: N
	Reference: Safety data sheet of L-(+)-Lactic Acid Purac
Conclusion	Adopt applicant´s revised version
Reliability	2
Acceptability	acceptable
Remarks	Appearance of a 93 % solution is indistinguishable from the appearance of an 88 % solution.

Date	2008/07/07

3.3 Appearance	
3.3.2 Colour	The correct quotation of the following field entries due to the safety data sheet is: Method: visual assessment Purity: 88 % L-(+)-Lactic acid Results: colourless to yellow light brown, ≤ 100 Apha GLP: N Reference: Safety data sheet of L-(+)-Lactic Acid Purac
Conclusion	Adopt applicant´s revised version
Reliability	2
Acceptability	acceptable
Remarks	Appearance of a 93 % solution is indistinguishable from the appearance of an 88 % solution.
Date	2008/07/07
3.3 Appearance	The correct quotation of the following field entries due to the safety data sheet is:
3.3.3 Odour	Method: olfactory assessment Purity: 88 % L-(+)-Lactic acid Results: characteristic GLP: N Reference: Safety data sheet of L-(+)-Lactic Acid Purac
Conclusion	Adopt applicant´s revised version
Reliability	2
Acceptability	acceptable
Remarks	Appearance of a 93 % solution is indistinguishable from the appearance of an 88 % solution.
Date	2008/07/07

3.4 Absorption spectra	3.4.a UV
UV/VIS	The correct quotation of the following field entries according to the given spectrum and literature is:
	Method: UV/VIS-method (Water)
	Purity: 93 % L-(+)-Lactic acid, Batch: 0712001825
	Results: 210 nm (0.12 % w/w L-(+)-Lactic acid in water)
	GLP: N
	Reference: R. Lieuwen, Labor journal 4, 6/2008.
	Reliability: 1
	3.4.b UV
	Method: UV/VIS-method
	Purity: Lactic acid, not stated
	Results: 210 nm
	Reference: C.H. Holten, Lactic acid, Verlag Chemie, Weinheim, 1971, S. 87-88.
	Reliability: 2
Conclusion	Adopt applicant´s revised version
Reliability	1
Acceptability	acceptable
Remarks	

Date	2008/07/07
3.4 Absorption spectra	3.4 IR
IR	The correct quotation of the following field entries according to the given spectrum and literature is:
	Method: FT-IR (Golden Gate ATR)
	Purity: 91 % L-(+)-Lactic acid, Batch: 0704002390
	Results: ν = 3600 cm^{-1} (OH), 3000 (CH), 2900 (OH), 1800 (C=O).
	GLP: N
	Reference: P. Klabbers, Labor journal 10, 10/2007
	Reliability: 1
	3.4 IR
	Method: IR
	Purity: Lactic acid, not stated
	Results: ν = 3620 - 3605 cm^{-1} (OH), 2980 - 2950 (CH), 3050 (OH), 1755 - 1720 (C=O).
	Reference: C.H. Holten, Lactic acid, Verlag Chemie, Weinheim, 1971, S. 89.
	Reliability: 2
Conclusion	Adopt applicant´s revised version

Reliability	1
Acceptability	acceptable
Remarks	

Date	2008/07/07
3.4 Absorption spectra	3.4. NMR
NMR	The correct quotation of the following field entries according to the given literature is: Method: ^{1}H-NMR (60 MHz, D_2O, TMS) Purity: 90 % L-(+)-Lactic acid Results: δ = 1.4 ppm (CH_3, d), 4.5 (CH, q), 1.4 (CH_3, extra peak), 4.5 (CH, superimposed quartet), 5.3 (CH, quartet), about 5 (OH). Remarks: additional peaks result from the formed Lactoyllactic acid GLP: N Reference: C.H. Holten, Lactic acid, Verlag Chemie, Weinheim, 1971, S. 518/519. 3.4 NMR Method: ^{1}H-NMR (60 MHz, D_2O, TMS) Purity: not stated (crystalline, L-(+)-Lactic acid) Results: δ = 1.4 ppm (CH_3, d), 4.4 (CH, q), 5.1 (OH, COOH, s) GLP: N Reference: C.H. Holten, Lactic acid, Verlag Chemie, Weinheim, 1971, S. 516/517
Conclusion	Adopt applicant´s revised version
Reliability	2
Acceptability	acceptable
Remarks	

Date	2008/07/07
3.4 Absorption spectra **MS**	The MS spectrum for the pure compound in the expert statement is copied from the NIST Chemistry WebBook. Further spectra of the manufactured active substance are submitted, so this spectrum is not accepted. The correct quotation of the following field entries according to the given spectra is: Method: GC-MS/ 2 MS-spectra (70 eV) Purity: 93 % L-(+)-Lactic acid, Batch 0712001825 Results: m/z (lactic acid) = 45 (COOH+) m/z (Lactoyl lactic acid) = 89 (lactoyl), 74 ($C_2H_2O_3$), 45 (COOH+). Remarks: no mother ion is detected in both spectra GLP: N Reference: R. Lieuwen, Labor journal 4, 6/2008.

Conclusion	Adopt applicant´s revised version
Reliability	1
Acceptability	acceptable
Remarks	

Date	2008/07/07
3.5 Solubility in water	3.5.a The correct quotation of the following field entries is: Method: not stated Purity: not stated, crystalline L-(+)-Lactic acid Results: completely miscible with water Remarks/Justification: No GLP-study was submitted. The given result of 86.1 % monomeric lactic acid is not valid. An equilibrium system of L-(+)-Lactic acid and its intermolecular esterification products is arised. No information is given if the equilibrium is complete. Therefore several constituents are existing in the aqueous medium which influences each other. That`s why the content of only monomeric L-(+)-Lactic acid does not state the complete water solubility. Reliability: 3 Reference: C.H. Holten, Lactic acid, Verlag Chemie, Weinheim, 1971, S. 53 3.5.b Remarks: The determination of the solubility in water of a 93 % active substance aqueous solution is not scientific. The test material is an aqueous solution itself. Furthermore no phase separation occurs during evaporation of water of lactic acid solutions of low concentration. Reference: Van Dongen (2007a) A 3.5-01
Conclusion	Adopt applicant´s revised version
Reliability	4
Acceptability	acceptable
Remarks	

Date	2008/07/07
3.6 Dissociation constant	The correct quotation of the following field entries is: Method: OECD 112 (conductometric method) Purity: not stated, crystalline L-(+)-Lactic acid Results: pKa = 3.86, T = 22.5 °C Reference: C.H. Holten, Lactic acid, Verlag Chemie, Weinheim, 1971, S. 62-67 GLP: N
Conclusion	Adopt applicant´s revised version
Reliability	2
Acceptability	acceptable

Remarks	The literature describes the conductometric method.
Date	2008/07/07
3.7 Solubility in organic solvents	The correct quotation of the following field entries is: Method: not stated Purity: not stated, crystalline L-(+)-Lactic acid Results: (T = 20 °C) 78.6 % wt in Methanol 29 % wt in 2-Ethylhexanol 0.005 % wt in Hexane 39.9 % wt in Ethylacetate 0.11 % wt in Toluene 38.7 % wt in Diethylether 52.9 % wt in 2-Butanone Remarks: Only the monomeric lactic acid (free acidity) is determined. Formed oligomers are not considered. The test substance is stirred for ¾ - 1 h at the given temperature and is directly analysed. No GLP study was submitted; therefore the given values can only be a rough estimation. Reference: J. v. Krieken, 1998, internal report.
Conclusion	Adopt applicant´s revised version
Reliability	2
Acceptability	acceptable
Remarks	
Date	2008/07/07
3.9 Partition coefficient n-octanol/water	3.9.a The correct quotation of the following field entries due to the submitted report is: Method: in house method (not described in detail in literature) Purity: crystalline L-Lactic acid Results: - 0.74 T = 20 °C GLP: N Reference: Gerorge P. van Lieshout 1997
Conclusion	Adopt applicant´s revised version
Reliability	2
Acceptability	acceptable
Remarks	
Date	2008/07/07

3.9 Partition coefficient n-octanol/water	3.9.b The determination of the partition coefficient n-octanol/water of a 93 % L-(+)-Lactic acid solution is not scientific, because of the existence of an equilibrium system of L-(+)-lactic acid with several oligomers.
Conclusion	Adopt applicant´s revised version
Reliability	4 (not applicable)
Acceptability	acceptable
Remarks	

Date	2009/03/01
3.10 Thermal stability, identity of relevant breakdown products	3.10 a The correct quotation of the following field entries due to the submitted report is: Method: In-house method Purity/Specification: LOTNo. 0202000748, 80 % L-(+)-Lactic acid Results: thermally stable up to 5 years (25 °C, 60 % RH) Remarks: maximal deviation of 1 % (rel.) in 5 years, stability behaviour of the 93 % concentrated L-(+)-Lactic acid is assumed not to differ Reliability: 2 Reference: Van Dongen (2007) – Purac Internal Data 3.10 b The correct quotation of the following field entries due to the submitted report is: Method: In-house method Purity/Specification: LOTNo. 2010400029, 90 % L-(+)-Lactic acid Results: thermally stable up to 5 years (25 °C, 60 % RH) thermally stable up to 1 year (40 °C, 75 % RH) Remarks: maximal deviation of 1 % (rel.) in the given time Reliability: 2 Reference: Van Dongen (2007) –Purac Internal Report

Conclusion	Adopt applicant´s revised version
Reliability	2
Acceptability	acceptable
Remarks	

Date	2009/03/01
3.13 Surface tension	For the determination of the surface tension according to the EU method 92/69/EEC A.5 a solution with 1 g substance in 1 l water has to be used. Therefore only the study with this concentration of lactic acid (0.093 %) can be used to determine the surface activity: The correct quotation of the following field entries due to the submitted report is: Method: 92/69/EC A.5 Purity: 92.8 % L-(+)-Lactic acid (concentration: 1 g / l in water), Batch 0712002519 GLP: Y Reference: Baltussen (2008)
Conclusion	
Reliability	1
Acceptability	acceptable
Remarks	

Date	2008/07/07
3.14 Viscosity	The viscosity of the 93 % L-(+)-Lactic acid is not experimentally determined. No further study is requested, because it is only an additional data. The viscosities of the diluted concentrations do not cover the present concentration.
Conclusion	
Reliability	4
Acceptability	acceptable
Remarks	

	COMMENTS FROM ...
Date	*Give date of comments submitted*
Results and discussion	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant´s summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A4.1 Analytical Methods for Detection and Identification

Annex Point IIA4.1/4.2 & IIIA-IV.1

			Official use only
		1 REFERENCE	
1.1	**Reference**	Holten, C.H. (1971) Lactic acid. Properties and Chemistry of Lactic Acid and Derivatives. Chapter XVIII: Analytical chemistry. Verlag Chemie GmbH, Weinheim/Bergstr. Germany. Not GLP, published..	x
1.2	**Data protection**	No	
1.2.1	Data owner	Not applicable	
1.2.2	Companies with letter of access	Not applicable	
1.2.3	Criteria for data protection	No data protection claimed	
		2 APPLICANT'S SUMMARY AND CONCLUSION	
2.1	**Summary**	In this chapter of the handbook for lactic acid, a review of analytic methods for lactic acid is provided.	
2.1.1	Reliability	2	
2.1.2	Deficiencies	Not applicable	

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2009/03/01
Materials and methods	No validation of the given methods is described. Further analytical methods are described in A4.1.
Conclusion	
Reliability	4
Acceptability	acceptable (not assignable)
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Results and discussion	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant´s summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*

Section A4.1 Analytical Methods for Detection and Identification

Annex Point IIA4.1/4.2 & IIIA-IV.1

Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A4.1 Analytical Methods for Detection and Identification

Annex Point IIA4.1/4.2 & IIIA-IV.1

			Official use only
		1 REFERENCE	
1.1	**Reference**	Anonymous (1968) Milchsäure, Acidium lacticum. In: Deutsches Arzneibuch, 7th edition, Deutscher Apotheker-Verlag, Stuttgart, Govi-Verlag GmbH, Frankfurt, p. 680-681. Not GLP, published.	x
1.2	**Data protection**	No	
1.2.1	Data owner	Not applicable	
1.2.2	Companies with letter of access	Not applicable	
1.2.3	Criteria for data protection	No data protection claimed	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Pharmacopoeia method	
2.2	**GLP**	No	
2.3	**Deviations**	Not applicable	
		3 MATERIALS AND METHODS	
3.1	**Preliminary treatment**		
3.1.1	Enrichment	Not applicable	
3.1.2	Cleanup	Not applicable	
3.2	**Detection**		
3.2.1	Separation method	Lactic acid is heated with 25 mL sodium hydroxide. Phenolphthalein is added and sodium hydroxide is titrated until the turning point is reached. Then, 2 mL hydrochloric acid is added and the solution is heated again. The excess is titrated back with sodium hydroxide.	
3.2.2	Detector	The total amount of sodium hydroxide used minus the total amount of hydrochloric acid equals the amount of lactic acid.1 mL of sodium hydroxide corresponds with 90.08 mg lactic acid.	
3.2.3	Standard(s)	Not applicable	
3.2.4	Interfering substance(s)	Not applicable	
3.3	**Linearity**		
3.3.1	Calibration range	Not mentioned (Pharmacopeia method)	
3.3.2	Number of measurements	Not mentioned (Pharmacopeia method)	
3.3.3	Linearity	Not mentioned (Pharmacopeia method)	

Section A4.1 Analytical Methods for Detection and Identification

Annex Point IIA4.1/4.2 & IIIA-IV.1

3.4	**Specifity: interfering substances**	Not applicable
3.5	**Recovery rates at different levels**	Not mentioned (Pharmacopeia method)
3.5.1	Relative standard deviation	Not mentioned (Pharmacopeia method)
3.6	**Limit of determination**	Not mentioned (Pharmacopeia method)
3.7	**Precision**	
3.7.1	Repeatability	Not mentioned (Pharmacopeia method)
3.7.2	Independent laboratory validation	Not mentioned (Pharmacopeia method)

4 APPLICANT'S SUMMARY AND CONCLUSION

4.1	**Materials and methods**	Lactic acid is heated with 25 mL sodium hydroxide. Phenolphthalein is added and sodium hydroxide is titrated until the turning point is reached. Then, 2 mL hydrochloric acid is added and the solution is heated again. The excess is titrated back with sodium hydroxide. The total amount of sodium hydroxide used minus the total amount of hydrochloric acid equals the amount of lactic acid.1 mL of sodium hydroxide corresponds with 90.08 mg lactic acid.
4.2	**Conclusion**	Pharmacopoeia methods meet the EU requirements for specificity, accuracy, precision and linearity. This method is suitable for analysis and identification of the active ingredient.
4.2.1	Reliability	1
4.2.2	Deficiencies	No

Section A4.1 Analytical Methods for Detection and Identification

Annex Point IIA4.1/4.2 & IIIA-IV.1

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2009/03/01
Materials and methods	No validation of the titration - method is described. No specify requirements are considered. Further analytical methods are described in Subsection A-4.1.
Conclusion	
Reliability	4
Acceptability	acceptable
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Results and discussion	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A4.1 Analytical Methods for Detection and Identification

Annex Point IIA4.1/4.2 & IIIA-IV.1

Official use only

	1 REFERENCE	
1.1	**Reference**	Klein, J. (2001) Assay of Lactic acid. Purac Document no. AMLAC009 Not GLP, Unpublished
1.2	**Data protection**	Yes
1.2.1	Data owner	Purac Biochem
1.2.2	Companies with letter of access	No
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing [a.s. / b.p.] for the purpose of its [entry into Annex I/IA / authorisation]
	2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Internal method
2.2	**GLP**	No
2.3	**Deviations**	Not applicable
	3 MATERIALS AND METHODS	
3.1	**Preliminary treatment**	
3.1.1	Enrichment	Not applicable
3.1.2	Cleanup	Not applicable
3.2	**Detection**	
3.2.1	Separation method	Lactic acid is neutralized by an excess of a sodium hydroxide solution. The excess is titrated back with hydrochloric acid. (Standardization of these solutions is described in Documents IV A4.1-03a and IV A4.1-03b)
3.2.2	Detector	Phenolphtalein is used as indicator.
3.2.3	Standard(s)	Not applicable
3.2.4	Interfering substance(s)	Not applicable
3.3	**Linearity**	
3.3.1	Calibration range	Not applicable
3.3.2	Number of measurements	Not applicable
3.3.3	Linearity	Not applicable
3.4	**Specifity: interfering substances**	Not applicable
3.5	**Recovery rates at different levels**	Not mentioned

Section A4.1 Analytical Methods for Detection and Identification

Annex Point IIA4.1/4.2 & IIIA-IV.1

3.5.1	Relative standard deviation	
3.6	**Limit of determination**	Not applicable
3.7	**Precision**	DOC IV A 4.1_11; Solution with a theoretical concentration of 91.3% lactic acid total. Determination of the content using method AMLAC009 by 7 independent technicians, all in duplicate.
3.7.1	Repeatability	Mean concentration (91.288 ± 0.12) %
3.7.2	Independent laboratory validation	Duplicate repeatability RSD 0.03 % Reproducibility RSD 0.06 %

4 APPLICANT'S SUMMARY AND CONCLUSION

4.1	**Materials and methods**	Lactic acid is neutralized by an excess of a sodium hydroxide solution. The excess is titrated back with hydrochloric acid. Phenolphtalein is used as the indicator.
4.2	**Conclusion**	The method is based on the method used by the QC laboratory of PURAC Biochem bv, Gorinchem. Method is intended to determine the actual (acid) concentration in solutions with a nominal concentration of 90-93% lactic acid. Due to the intended application of the method, no interferences are expected, and no analytical identification is required. The method has an acceptable repeatability and reproducibility.
4.2.1	Reliability	1
4.2.2	Deficiencies	No

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2009/12/14
Materials and methods	The given titration method is not specific, only in addition to the chromatographically methods it is acceptable to be used. Because of the validation of the chromatographically method no further information is required.
Conclusion	Adopt applicant´s version
Reliability	2
Acceptability	acceptable (because of further analytical methods)
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Results and discussion	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant´s summary and conclusion.* *Discuss if deviating from view of rapporteur member state*

Section A4.1 Analytical Methods for Detection and Identification

Annex Point IIA4.1/4.2 & IIIA-IV.1

Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A4.1 Analytical Methods for Detection and Identification

Annex Point IIA4.1/4.2 & IIIA-IV.1

			Official use only
		1 REFERENCE	
1.1	**Reference**	Rodriguez, E. (2001) Manual of analytical procedures of lactic acid; Determination of lactic acid content (PSP). Purac Document no. LA008C Not GLP, Unpublished	
		Escribà, J. (2001) Validation report of the method for determination of lactic acid content (PSP method) LA008 Purac Document no. VAL-LA008(I) and VAL-LA008-1(I) Not GLP, Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Purac Biochem	
1.2.2	Companies with letter of access	No	
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing [a.s. / b.p.] for the purpose of its [entry into Annex I/IA / authorisation]	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Internal method	
2.2	**GLP**	No	
2.3	**Deviations**	Not applicable	
		3 MATERIALS AND METHODS	
3.1	**Preliminary treatment**		
3.1.1	Enrichment	Not applicable	
3.1.2	Cleanup	Not applicable	
3.2	**Detection**		
3.2.1	Separation method	Not applicable.	
3.2.2	Detector		
3.2.3	Standard(s)		
3.2.4	Interfering substance(s)	Other acids; not relevant since the composition of the sample is under strict control.	
3.3	**Linearity**		
3.3.1	Calibration range	0.77 – 1.19 g total lactic acid with internal method; 0.86 – 1.0 g total lactic acid with single-step method (only total acid).	
3.3.2	Number of measurements	Not mentioned	
3.3.3	Linearity	r = 0.999991 with internal method.	
3.4	**Specifity: interfering**	Other acids; not relevant since the composition of the sample is under strict control.	

Formatiert: Hervorheben

Formatiert: Hervorheben

	substances		
3.5	**Recovery rates at different levels**	Recovery 100.02% @ 90.03% acid content with internal method; recovery 99.98% @ 90.03% acid content with single-step method (only total acid).	
3.5.1	Relative standard deviation	*0.078% with internal method; 0.044% with single step method.*	
3.6	**Limit of determination**	Not relevant.	
3.7	**Precision**		
3.7.1	Repeatability	90.05 ± 0.078% @ 90.% acid content with internal method; 90.013 ± 0.044% @ 90.03% acid content with single-step method (only total acid).	
3.7.2	Independent laboratory validation	Not relevant	
		4 APPLICANT'S SUMMARY AND CONCLUSION	
4.1	**Materials and methods**	Note that this is a method for determining content; as such samples can always be pretreated to contain an amount that falls within the limits of the method. Linearity, recovery at different levels, and LoQ of such a method are therefore not relevant.	x
4.2	**Conclusion**	The method is based on the method used by the QC laboratory of PURAC Biochem bv, Gorinchem.	
4.2.1	Reliability	1	
4.2.2	Deficiencies	No	

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2009/08/21
Materials and methods	
Conclusion	Adopt applicant´s version
Reliability	2
Acceptability	acceptable
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*

Section A4.1 Analytical Methods for Detection and Identification

Annex Point IIA4.1/4.2 & IIIA-IV.1

Results and discussion	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant s summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A4.1 Analytical Methods for Detection and Identification

Annex Point IIA4.1/4.2 & IIIA-IV.1

Official use only

1 REFERENCE

1.1	**Reference**	Huntink, T.B. (2005) Determination of the chiral purity [redacted] Purac Document no. RDT/A/0003 Not GLP, Unpublished Van Nieuwenhuizen, S. (1999) Determination of the chiral purity of lactic acid and derivatives with GLC Thesis, Hogeschool van Rotterdam Not GLP, Unpublished Method validation
1.2	**Data protection**	Yes
1.2.1	Data owner	Purac Biochem
1.2.2	Companies with letter of access	No
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing [a.s. / b.p.] for the purpose of its [entry into Annex I/IA / authorisation]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Internal method
2.2	**GLP**	No
2.3	**Deviations**	Not applicable

3 MATERIALS AND METHODS

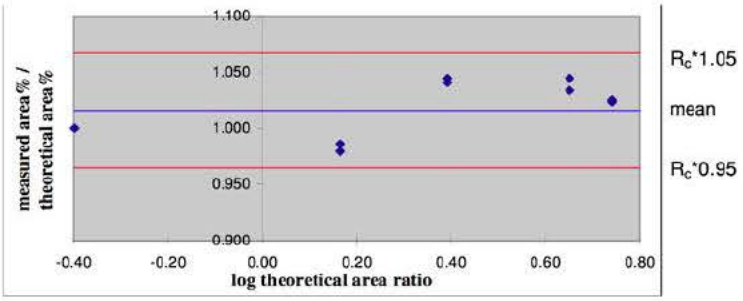
3.1	**Preliminary treatment**	
3.1.1	Enrichment	Not applicable
3.1.2	Cleanup	[redacted]
3.2	**Detection**	
3.2.1	Separation method	[redacted]
3.2.2	Detector	[redacted]
3.2.3	Standard(s)	Lactic acid with a known S-to-L lactate ratio, in the 0.1 to 1.5% range.
3.2.4	Interfering substance(s)	None; [redacted]
3.3	**Linearity**	
3.3.1	Calibration range	A normal calibration range is not applicable. Note that the method is not intended for quantitation of an amount, but only of a ratio. As such the method can be done at a single, appropriate response point, and has its

Section A4.1 Analytical Methods for Detection and Identification

Annex Point IIA4.1/4.2 & IIIA-IV.1

own internal standard.

[redacted]



3.3.2	Number of measurements	9
3.3.3	Linearity	$r^2 = 0.9996$
3.4	**Specifity: interfering substances**	None:

[redacted]

3.5	**Recovery rates at different levels**	
3.5.1	Relative standard deviation	95.3 ± 1.5 % @ 0.5% chiral impurity 101.1 ± 0.5 % @ 1.25% chiral impurity 101.6 ± 0.6 % @ 3.1% chiral impurity
3.6	**Limit of determination**	0.04% chiral impurity.
3.7	**Precision**	
3.7.1	Repeatability	0.38%
3.7.2	Independent laboratory validation	Not applicable.

Section A4.1 Analytical Methods for Detection and Identification

Annex Point IIA4.1/4.2 & IIIA-IV.1

4 APPLICANT'S SUMMARY AND CONCLUSION

4.1 Materials and methods

[redacted]

4.2 Conclusion

[redacted]

4.2.1 Reliability 1

4.2.2 Deficiencies No

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2009/08/21
Materials and methods	
Conclusion	Adopt applicant´s version
Reliability	1
Acceptability	acceptable
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Results and discussion	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant´s summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A4.1 Analytical Methods for Detection and Identification

Annex Point IIA4.1/4.2 & IIIA-IV.1

Official use only

1 REFERENCE

1.1	**Reference**	Iking, M. (2007) Quantification of the total amount of organic acids and ethanol [redacted] Purac Document no. RDT/A/003 Not GLP, Unpublished Validation: De Jong, V. (2008) Measurement uncertainty for organic acids and oligomers. Purac Document no. VdJ2009058 Not GLP, Unpublished
1.2	**Data protection**	Yes
1.2.1	Data owner	Purac Biochem
1.2.2	Companies with letter of access	No
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing [a.s. / b.p.] for the purpose of its [entry into Annex I/IA / authorisation]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Internal method
2.2	**GLP**	No
2.3	**Deviations**	Not applicable

3 MATERIALS AND METHODS

3.1	**Preliminary treatment**	
3.1.1	Enrichment	Not applicable
3.1.2	Cleanup	[redacted]
3.2	**Detection**	
3.2.1	Separation method	[redacted]
3.2.2	Detector	[redacted]
3.2.3	Standard(s)	[redacted]
3.2.4	Interfering substance(s)	Not applicable
3.3	**Linearity**	
3.3.1	Calibration range	[redacted]

Section A4.1 Analytical Methods for Detection and Identification

Annex Point IIA4.1/4.2 & IIIA-IV.1

[redacted]

3.3.2 Number of measurements

[redacted]

3.3.3 Linearity

[redacted]

3.4 Specifity: interfering substances

Not relevant [redacted].

3.5 Recovery rates at different levels

[redacted]

3.5.1 Relative standard deviation

3.6 Limit of determination

[redacted]

3.7 Precision

3.7.1 Repeatability

[redacted]

Section A4.1 Analytical Methods for Detection and Identification

Annex Point IIA4.1/4.2 & IIIA-IV.1

[redacted]

3.7.2	Independent laboratory validation	Not applicable

4 APPLICANT'S SUMMARY AND CONCLUSION

4.1	**Materials and methods**	[redacted]
4.2	**Conclusion**	The method is suitable as in-house method for quality control. Method is suitable as method to determine impurities in lactic acid samples.
4.2.1	Reliability	1
4.2.2	Deficiencies	No

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2008/08/21
Materials and methods	
Conclusion	Adopt applicant´s version
Reliability	1
Acceptability	acceptable
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Results and discussion	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant´s summary and conclusion.* *Discuss if deviating from view of rapporteur member state*

Section A4.1 Analytical Methods for Detection and Identification

Annex Point IIA4.1/4.2 & IIIA-IV.1

Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A4.1 Analytical Methods for Detection and Identification

Annex Point IIA4.1/4.2 & IIIA-IV.1

Official use only

1 REFERENCE

1.1	**Reference**	Lieuwen, R. (2008) Determination of lactide, [redacted] Purac Document no. RDT/A/0036 Not GLP, Unpublished De Jong, V. (2008) Measurement uncertainty for organic acids [redacted]. Purac Document no. VdJ2009058 Not GLP, Unpublished
1.2	**Data protection**	Yes
1.2.1	Data owner	Purac Biochem
1.2.2	Companies with letter of access	No
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing [a.s. / b.p.] for the purpose of its [entry into Annex I/IA / authorisation]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Internal method
2.2	**GLP**	No
2.3	**Deviations**	Not applicable

3 MATERIALS AND METHODS

3.1	**Preliminary treatment**	
3.1.1	Enrichment	Not applicable
3.1.2	Cleanup	[redacted]
3.2	**Detection**	
3.2.1	Separation method	[redacted]
3.2.2	Detector	[redacted]
3.2.3	Standard(s)	Lactic acid, [redacted]
3.2.4	Interfering substance(s)	Not applicable
3.3	**Linearity**	
3.3.1	Calibration range	[redacted]

Section A4.1 Analytical Methods for Detection and Identification

Annex Point IIA4.1/4.2 & IIIA-IV.1

3.3.2	Number of measurements	[redacted] lactic acid: 6 [redacted]
3.3.3	Linearity	[redacted] lactic acid: linear over entire calibration range ($r^2 \geq 0.9999$) [redacted]
3.4	**Specifity: interfering substances**	Not applicable
3.5	**Recovery rates at different levels**	[redacted] Cannot be ascertained from study. [redacted]
3.5.1	Relative standard deviation	*See repeatability*
3.6	**Limit of determination**	[redacted] Note that this method is a research method, [redacted]
3.7	**Precision**	
3.7.1	Repeatability	[redacted] lactic acid: 5% [redacted]
3.7.2	Independent laboratory validation	Not applicable

4 APPLICANT'S SUMMARY AND CONCLUSION

4.1	**Materials and methods**	[redacted]

Section A4.1 Analytical Methods for Detection and Identification

Annex Point IIA4.1/4.2 & IIIA-IV.1

4.2	**Conclusion**	[redacted] The methods are suitable as an in-house quality control method. [redacted]
4.2.1	Reliability	1
4.2.2	Deficiencies	No

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2009/08/21
Materials and methods	
Conclusion	Adopt applicant´s version
Reliability	1
Acceptability	acceptable
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Results and discussion	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant´s summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A4.1 Analytical Methods for Detection and Identification

Annex Point IIA4.1/4.2 & IIIA-IV.1

Official use only

1 REFERENCE

1.1	**Reference**	Van Nieuwenhuizen, S. (1999) Determination of the chiral purity of lactic acid and derivatives [redacted] Thesis, Hogeschool van Rotterdam Not GLP, Unpublished
1.2	**Data protection**	Yes
1.2.1	Data owner	Purac Biochem
1.2.2	Companies with letter of access	No
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing [a.s. / b.p.] for the purpose of its [entry into Annex I/IA / authorisation]

2 GUIDELINES AND QUALITY ASSURANCE

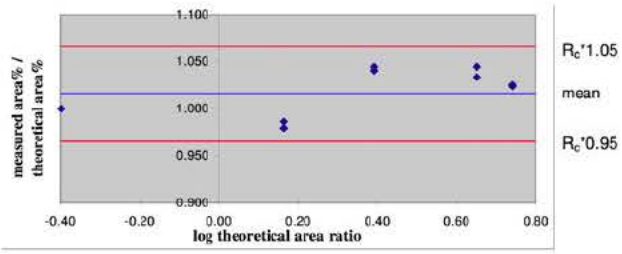
2.1	**Guideline study**	This thesis forms the basis and validation for the chiral purity method described in A4_1_06.
2.2	**GLP**	No
2.3	**Deviations**	Not applicable

3 MATERIALS AND METHODS

3.1	**Preliminary treatment**	
3.1.1	Enrichment	See A4_1_06.
3.1.2	Cleanup	See A4_1_06.
3.2	**Detection**	
3.2.1	Separation method	See A4_1_06.
3.2.2	Detector	See A4_1_06.
3.2.3	Standard(s)	See A4_1_06.
3.2.4	Interfering substance(s)	None; [redacted]
3.3	**Linearity**	
3.3.1	Calibration range	[redacted] all the points are lying between the 5% deviation lines (Rc*1.05 and Rc*0.95). So there can be concluded that all the points over the range of 0.1 until 5.5% chiral impurity have a linear relation.

Section A4.1 Analytical Methods for Detection and Identification

Annex Point IIA4.1/4.2 & IIIA-IV.1



3.3.2	Number of measurements	9
3.3.3	Linearity	$r^2 = 0.9996$
3.4	**Specifity: interfering substances**	None:

Table 4: peak table samples in S-form

component	retention time [min]
methyl-(R)-lactate	5.68
methyl-(S)-lactate	6.18

Table 5: peak table samples in R-form

component	retention time [min]
methyl-(R)-lactate	5.57
methyl-(S)-lactate	6.29

Table 6: list of possible impurities with their retention times

impurity	retention time [min]
methanol/methyl formate	1.72
methyl acetate	1.89
n-propyl alcohol	2.48
cyclohexane	3.23
methyl pyruvate	3.48
isobutyl alcohol	3.93
n-butyl alcohol	4.23
methyl 2-methoxy propanoate 1	4.57
methyl 2-methoxy propanoate 2	4.88
methyl 2-formyloxy propanoate 1	6.17 *
methyl 2-formyloxy propanoate 2	7.75
methyl 2-acetoxy propanoate	8.06
methyl 2-hydroxy butyrate 1	8.66
methyl 2-hydroxy butyrate 2	9.08
methyl 2-hydroxy isovalerate	9.44
n-propyl lactate	10.94
2-methoxy propanoic acid	11.26
dimethyl succinate	12.50
methyl lactoyl lactate	12.60
isobutyl lactate	12.69
n-butyl lactate	13.20

3.5 Recovery rates at different levels Not applicable

3.5.1 Relative standard deviation

Section A4.1 Analytical Methods for Detection and Identification

Annex Point IIA4.1/4.2 & IIIA-IV.1

3.6 Limit of determination

RSD and the confidence interval of each component

sample	mean % of chiral imp.	standard deviation	RSD [%]	confidence interval	limit of detection [% (area/area)]	limit of quantitation [% (area/area)]
IBL	1.01	6.325 E-03	0.63	0.005	0.05	0.11
PL	0.88	5.270 E-03	0.60	0.004	0.03	0.05
BL	0.91	4.743 E-03	0.52	0.003	0.04	0.06
NaL	0.73	5.270 E-03	0.73	0.004	0.04	0.07
APA	0.41	4.216 E-03	1.02	0.003	0.04	0.08
HL	1.27	4.830 E-03	0.38	0.004	0.02	0.04

Since the determination of an absolute amount or concentration is not the objective of this method, samples can always be analysed at the optimum method response point; LoD therefore is not applicable.

3.7 Precision

3.7.1 Repeatability

Table 3.7.1: calculation of the recovery

sample name:	measured area ratio [%]		theoretical area ratio [%]		recovery
	R-HL	S-HL	R-HL	S-HL	[%]
VALAC04	1.26	98.74	1.25	98.75	100.80
VALAC05	1.26	98.74	1.25	98.75	100.80
VALAC06	1.27	98.73	1.25	98.75	101.60
VALAC07	3.14	96.86	3.10	96.90	101.29
VALAC08	3.14	96.86	3.10	96.90	101.29
VALAC09	3.17	96.83	3.10	96.90	102.26
VALAC10	0.47	99.53	0.50	99.50	94.00
VALAC11	0.48	99.52	0.50	99.50	96.00
VALAC12	0.48	99.52	0.50	99.50	96.00

3.7.2 Independent laboratory validation: Not applicable

4 APPLICANT'S SUMMARY AND CONCLUSION

4.1 Materials and methods

4.2 Conclusion

[redacted]

4.2.1 Reliability: 1

4.2.2 Deficiencies: No

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*2014-10-30*
Materials and methods	

Section A4.1 Analytical Methods for Detection and Identification

Annex Point IIA4.1/4.2 & IIIA-IV.1

Conclusion	*The information given above is only in addition to the analytical methods for detection and identification presented in the other DOC III A 4.1.06 documents.* *It would be more useful and comprehensible to merge all information on the analytical methods for detection and identification and their validation in one DOC III A 4.1.06*
Reliability	
Acceptability	
Remarks	*Additional information.*
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Results and discussion	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant s summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Formatiert: Englisch (Großbritannien)

Section A4.1 Analytical Methods for Detection and Identification

Annex Point IIA4.1/4.2 & IIIA-IV.1

Official use only

1 REFERENCE

1.1	**Reference**	De Jong, V. (2008) Measurement uncertainty for organic acids and oligomers. Purac Document no. VdJ2008097 Not GLP, Unpublished
1.2	**Data protection**	Yes
1.2.1	Data owner	Purac Biochem
1.2.2	Companies with letter of access	No
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing [a.s. / b.p.] for the purpose of its [entry into Annex I/IA / authorisation]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Internal method
2.2	**GLP**	No
2.3	**Deviations**	Not applicable

3 MATERIALS AND METHODS

3.1	**Preliminary treatment**	
3.1.1	Enrichment	This is a validation study [redacted]
3.1.2	Cleanup	This is a validation study [redacted]
3.2	**Detection**	
3.2.1	Separation method	[redacted] This is a validation study [redacted]
3.2.2	Detector	[redacted] This is a validation study [redacted]

Section A4.1 Analytical Methods for Detection and Identification

Annex Point IIA4.1/4.2 & IIIA-IV.1

[redacted]

3.2.3	Standard(s)	This is a validation study [redacted]
3.2.4	Interfering substance(s)	Not applicable
3.3	**Linearity**	
3.3.1	Calibration range	[redacted] Relevant range; note that this is a method for quantifying impurities in a technical product; as such, samples can be prepared to always fall within the required calibration range. [redacted] Relevant range; note that this is a method for quantifying impurities in a technical product; as such, samples can be prepared to always fall within the required calibration range.
3.3.2	Number of measurements	[redacted] formic acid: 11 acetic acid: 11 2-hydroxybutyric acid: 9 pyruvic acid: NA [redacted] lactic acid: 6 lactoyl-lactide: 6 lactide: 6 meso-lactide: 6
3.3.3	Linearity	[redacted] formic acid: linear over entire calibration range (r = 0.9999) acetic acid: linear over entire calibration range (r^2 = 0.9994) 2-hydroxybutyric acid: linear over entire calibration range (r^2 = 0.9999) [redacted] lactic acid: linear over entire calibration range ($r^2 \geq 0.9999$) lactoyl-lactide: linear over entire calibration range ($r^2 \geq 0.9999$) lactide: linear over entire calibration range ($r^2 \geq 0.9999$) meso-lactide: linear over entire calibration range ($r^2 \geq 0.9999$)
3.4	**Specifity: interfering substances**	Not applicable
3.5	**Recovery rates at different levels**	[redacted] lactic acid: 100.7% at method concentration acetic acid: 101.0% at method concentration [redacted]

Section A4.1 Analytical Methods for Detection and Identification

Annex Point IIA4.1/4.2 & IIIA-IV.1

[redacted]

3.5.1 Relative standard deviation: *See repeatability*

3.6 Limit of determination

3.7 Precision

3.7.1 Repeatability

[redacted]
lactic acid: 3.1%
acetic acid: 4.7%
[redacted]

[redacted]
lactic acid: 5%
lactoyl-lactide: 3.8%
lactide: 2.8%
meso-lactide: 2.0%

3.7.2 Independent laboratory validation: Not applicable

4 APPLICANT'S SUMMARY AND CONCLUSION

4.1 Materials and methods

[redacted]

[redacted]

4.2 Conclusion: The methods are suitable as an in-house quality control method. Method A4.1-07 is suitable as method to determine impurities in lactic acid samples.

4.2.1 Reliability: 1

4.2.2 Deficiencies: No

Evaluation by Competent Authorities

Section A4.1 Analytical Methods for Detection and Identification

Annex Point IIA4.1/4.2 & IIIA-IV.1

	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*30/10/2014*
Materials and methods	
Conclusion	*The information given above is only in addition to the analytical methods for detection and identification presented in the DOC III A 4.1.07 and Doc III A4.1.08 documents.* *It would be more useful and comprehensible to merge all information on one analytical method for detection and identification and their validation in one DOC III A 4.1 document*
Reliability	
Acceptability	
Remarks	*Additional information.*
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Results and discussion	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant´s summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A4.2 Analytical Methods for Detection and Identification

Annex Point IIA4.1/4.2 & IIIA-IV.1

Official use only

1 REFERENCE

1.1	**Reference**	Klein, J. (2007) Lactic acid in earth Purac Document no. AMENV001 Not GLP, Unpublished
1.2	**Data protection**	Yes
1.2.1	Data owner	Purac Biochem
1.2.2	Companies with letter of access	No
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing [a.s. / b.p.] for the purpose of its [entry into Annex I/IA / authorisation]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Internal method
2.2	**GLP**	No
2.3	**Deviations**	Not applicable

3 MATERIALS AND METHODS

3.1	**Preliminary treatment**	
3.1.1	Enrichment	Not applicable
3.1.2	Cleanup	Not applicable
3.2	**Detection**	
3.2.1	Separation method	[redacted]
3.2.2	Detector	[redacted]
3.2.3	Standard(s)	Lactic acid standard solution
3.2.4	Interfering substance(s)	Not applicable
3.3	**Linearity**	
3.3.1	Calibration range	4.9-32.3 mg/g soil
3.3.2	Number of measurements	8
3.3.3	Linearity	Not mentioned
3.4	**Specifity: interfering substances**	Not applicable

Section A4.2 Analytical Methods for Detection and Identification

Annex Point IIA4.1/4.2 & IIIA-IV.1

3.5	**Recovery rates at different levels**	88-101%
3.5.1	Relative standard deviation	Not mentioned
3.6	**Limit of determination**	Not mentioned
3.7	**Precision**	
3.7.1	Repeatability	Not mentioned
3.7.2	Independent laboratory validation	Not mentioned

4 APPLICANT'S SUMMARY AND CONCLUSION

4.1	**Materials and methods**	[redacted]
4.2	**Conclusion**	The method shows a recovery rate of 88-101% and is suitable fordetermining lactic acid in soil samples.
4.2.1	Reliability	2
4.2.2	Deficiencies	No

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2014/06/23
Materials and methods	The acceptability of the method of Klein /2007 cannot be judged because fundamental validation data are missing.
Conclusion	No relevant residues of L(+) lactic acid in soil are expected. Analytical methods for L(+) lactic acid in soil are not required.
Reliability	4
Acceptability	not acceptable
Remarks	none
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Results and discussion	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*

Section A4.2 Analytical Methods for Detection and Identification

Annex Point IIA4.1/4.2 & IIIA-IV.1

Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section 4.3 Annex Point IIA4.3	Analytical methods for residues in/on food or feedstuffs	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [ ]** **Other justification [x]**	
Detailed justification:	According to the 'Technical Guidance Document on data requirements', this is an additional data requirement. Although lactic acid will be used in PT3 and PT4, no residues in food/feed are expected. Furthermore, the food products involved contain a naturally high background concentration of lactic acid. PT3: Indirect exposure via residues in milk are not expected. Teat dipping with Filmadine occurs after milking, and it is assumed that possible residues on teats have been completely broken down at the next milking event. PT4: Secondary exposure of the general public may occur via residues in beer, due to the cleaning procedure. However, as the tank is rinsed with drinking water after cleaning with Deptacid 2D, no residues are expected. Furthermore, it should be noted that lactic acid is a natural component of beer; concentrations of 10-1000mg/L have been reported (Klopper et al. (1986), see the expert statement on lactic acid, included in the dossier as A6.2-01). Therefore, the dietary exposure to lactic acid via beer is not considered to be a problem.	
Undertaking of intended data submission [ ]	Not applicable	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	2014/06/23	
Evaluation of applicant's justification	Applicant's justification is adopted.	
Conclusion	Applicant's justification is acceptable. Relevant residues in food or fedding stuffs resulting from the use of L(+) lactic acid are not expected.Analytical methods for L(+) lactic acid in food or feeding stuffs are not required.	
Remarks	No	

Section 4.3 Annex Point IIA4.3	Analytical methods for residues in/on food or feedstuffs	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Section A5	Effectiveness against target organisms and intended uses	
Subsection (Annex Point)		**Official use only**
5.1 Function (IIA5.1)	Code MG01: Disinfectants, general biocidal products. Product types: PT2: Private and public area disinfectant PT3: Disinfectant for veterinary hygiene PT4: Disinfectant for food and feed areas Code MG02: Preservatives PT6: In-can preservative	x
5.2 Organism(s) to be controlled and products, organisms or objects to be protected (IIA5.2)		
5.2.1 Organism(s) to be controlled (IIA5.2)	Bacteria	
5.2.2 Products, organisms or objects to be protected (IIA5.2)	PT2: Disinfection of surfaces in bathrooms PT3: Udder hygiene PT4: Disinfection in brewery industry PT6: Preservation of fabric conditioner, and manual dishwashing liquid	x
5.3 Effects on target organisms, and likely concentration at which the active substance will be used (IIA5.3)		
5.3.1 Effects on target organisms (IIA5.3)	General publication on effect on target organisms and mode of action included in Document IV as A5/01: Alakomi, H.-L., Skyttä, E., Saarela, M., Mattila-Sandholm, T., Latva-Kala, K., Helander, I.M. (2000). Lactic acid permeabilizes Gram-negative bacteria by disrupting the outer membrane. Applied and Environmental Microbiology, Vol. 66, No.5, p.2001-2005. Combined effect: - Lowering pH by penetrating the cytoplasmatic membrane of bacteria, resulting in reduced intracellulat pH and disruption of the transmembrane proton motive force - Function as permeabilizer of the gram-negative bacterial outer membrane.	x

5.3.2	**Likely concentrations at which the A.S. will be used (IIA5.3)**		x
	PT2	2%	
	PT3	8%	
	PT4	4%	
	PT6	0.05-1 %	
5.4	**Mode of action (including time delay) (IIA5.4)**		
5.4.1	**Mode of action**	General publication on effect on target organisms and mode of action included in Document IV as A5/01:	
		Alakomi, H.-L., Skyttä, E., Saarela, M., Mattila-Sandholm, T., Latva-Kala, K., Helander, I.M. (2000). Lactic acid permeabilizes Gram-negative bacteria by disrupting the outer membrane. Applied and Environmental Microbiology, Vol. 66, No.5, p.2001-2005.	
		Combined effect:	
		- Lowering pH by penetrating the cytoplasmatic membrane of bacteria, resulting in reduced intracellulat pH and disruption of the transmembrane proton motive force	x
		- Function as permeabilizer of the gram-negative bacterial outer membrane.	
5.4.2	**Time delay**	Not relevant.	
5.5	**Field of use envisaged (IIA5.5)**		
	MG01: Disinfectants, general biocidal products	PT2: Disinfection of surfaces in bathrooms	
		PT3: Udder hygiene	
		PT4: Disinfection of surfaces in slaughter houses and milking industry.	x
	MG02: Preservatives	PT6: In-can preservative in fabric conditioner, and manual dishwashing liquid.	
	MG03: Pest control	Not applicable	
	MG04: Other biocidal products	Not applicable	
	Further specification	Not applicable	
5.6	**User (IIA5.6)**		
	Industrial	PT4: Disinfection in brewery industry	
	Professional	PT3: Udder hygiene	

	General public	PT2: Disinfection of surfaces in bathrooms PT6: In-can preservatives
5.7	**Information on the occurrence or possible occurrence of the development of resistance and appropriate management strategies (IIA5.7)**	
5.7.1	**Development of resistance**	No development of resistance expected.
5.7.2	**Management strategies**	No development of resistance expected.
5.8	**Likely tonnage to be placed on the market per year (IIA5.8)**	2-5 ton

Section A5	Effectiveness against target organisms and intended uses

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2015/01/22
Conclusion	
Remarks	*The comments by the RMS refer to PT1 even tough the document by the applicant contains information for PT1, 2, 3, 4 and 6. The specific comments regarding PT 2, 3, 4 and 6 can be found in the corresponding CARs.* 5.1: additionally PT1 (Disinfectants for human hygiene) is applied for 5.2.2; 5.5: additionally: PT1: hands disinfection 5.3.1: In this chapter, a short summary of the efficacy data is helpful: The dummy product (containing 3% Lactic Acid and 2.5% SLeS) shows a basic bactericidal activity after a contact time of 5 min according to EN 1276:2009. Additionally, it was shown that 2.5% SLeS is not effective if used alone. Therefore, a basic bactericidal activity of 3% Lactic Acid can be concluded. The study performed is sufficient at the approval stage of the substance. 5.3.2: PT1: 3% 5.4.1: The undissociated form of lactic acid is able to penetrate the cytoplasmatic membrane of bacteria, resulting in a reduction of the intracellular pH and disruption of the transmembrane proton motive force.
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Results and discussion	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant´s summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	