

## Certification of Substances Division

<b>Title:</b>	<b>The EDQM position on CEP Applications for Biological Substances</b>
<b>Reference Document:</b>	<b>PA/PH/CEP (09) 152 rev 01 (EN)</b>

According to Resolution AP-CSP (07)1, the procedure for 'Certification of Suitability to the Monographs of the European Pharmacopoeia' (CEPs) is intended for substances for which a monograph, either general or specific, has been adopted by the European Pharmacopoeia Commission. The procedure does not apply for direct gene products (i.e. proteins), products obtained from human tissues, vaccines and blood products and preparations.

In light of the discussions held at the European level concerning the classification of biological products, the EDQM has decided to exclude from the scope of the procedure those products that have been classified, by the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMD(h)), as "other biological substances". A list is available from the website of the Heads of Medicines Agencies [http://www.hma.eu/fileadmin/dateien/Human\\_Medicines/CMD\\_h\\_/procedural\\_guidance/Compilation\\_Biological\\_Active\\_Substance\\_non-recombinant\\_origin.pdf](http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Compilation_Biological_Active_Substance_non-recombinant_origin.pdf).

The reasoning behind this decision is as follows: the characterization and determination of biological substances require not only a combination of physico-chemical and biological testing, but also extensive knowledge of the production process and its control.

The EDQM, therefore, will not accept any new application for CEPs for these biological substances.

Existing CEPs are not affected by this decision.

**OVERVIEW OF BIOLOGICAL ACTIVE SUBSTANCES OF NON-RECOMBINANT ORIGIN**

*June 2007*

This table is a non-exhaustive list of biological active substances/biological medicinal products that do not belong to one of the categories that are already considered as biological active substances/biological medicinal products by default in the current legislation (such as: recombinant proteins, monoclonal antibodies, blood products, immunological medicinal products such as sera and vaccines, allergens, and advanced technology products such as gene and cell therapy products).

<b>Active ingredient</b>	<b>Type of substance, source</b>	<b>Administration route</b>	<b>Trade names (not exhaustive)</b>	<b>EU-procedure number</b>
Human chorionic gonadotrophin <sup>1)</sup>	Glycoproteine, extract from human urine	Injection, IM, SC	Pregnyl, 500/1500/5000 IE Pregnyl // 5000IE Choragon 1500 Choragon 5000	
Menotrophin	FH/FSH extract from human urine	Injection, IM, SC	Humegon 75/150IE Menegon 150 HMG Ferring 150 Menopur 75	
Urofollitrophin <sup>1)</sup>	FSH extract from human urine	Injection SC	Bravelle 75 IE Fostimon	UK/H/697 FR/H/282
Streptokinase, <sup>1)</sup>	Protein from Streptococcus cultures	Injection IV, topical	Streptase 100/250/750/1500 kIE	
Streptodornase	Protein from Streptococcus cultures	Injection IV		
Urokinase <sup>1)</sup>	Tissue culture of human renal human renal cells	Injection IV	Medacinase 10/50/100/250/500 kIE Urokinase-Kabi 50/100/250/500 kIE	
Aprotinin <sup>1)</sup>	Polypeptide from bovine lung	Injection IV Recently also as component of fibrine glues	Trasylo1 500.000 IE	
Hyaluronidase <sup>1)</sup>	Extract from bovine or ovine testes	Injection eye	Hyason	
Protamine <sup>1)</sup>	Polypeptide from sperma/testes of fish species	Injection IV, IM	Protamine 1000/5000 'ICN' Protamine Leo Pharma	SE/H/562

Active ingredient	Type of substance, source	Administration route	Trade names (not exhaustive)	EU-procedure number
Botulinum toxin Type A <sup>2)</sup>	Protein from Clostridium botulinum culture	Injection, IM	Botox 100E Dysport 500E Vistabel	FR/H/230
Botulinum toxin Type B	Protein from Clostridium botulinum	Injection, IM	Neurobloc 5000 IE/ml	EMEA/H/C/301
Tuberculin <sup>2)</sup>	Filtrate Mycobac.tub culture	Injection intracutaneous	Tuberculine PPDRT23 SSI	
BCG for bladder instillation <sup>2)</sup>	M. bovis, var. BCG	Intravesical	BCG-medac Immucyst Onco-Tice	DE/H/001 DE/H/367
→ Heparin <sup>1)</sup>	Heparin,	Injection IV SC	Heparine Leo	
Chondroitin sulphate sodium	heparin	Oral	Condral/Condrosulf	
→ Dalteparine <sup>1)</sup>	LMM heparin	Injection IV SC	Fragmin; Dalteparin Pfizer	SE/H/549
→ Enoxaparine <sup>1)</sup>	LMM heparin	Injection SC	Clexane	
Nadroparine <sup>1)</sup>	LMM heparin	Injection SC	Fraxiparine; Fraxodi; Nadroperin GSK	DE/H/809
Tinzaparine <sup>1)</sup>	LMM heparin	Injection SC	Innohep	
Reviparin <sup>1)</sup>	LMM heparin	Injection SC	Clivarin	SE/H/524
Parnaparine <sup>1)</sup>	LMM heparin	Injection SC	Fluxum	
Certoparine <sup>1)</sup>	LMM heparin	---	---	
Danaparoid sodium <sup>1)</sup>	Mixed glucosaminoglucans	Injection SC	Orgaran	NL/H/142
Sodium hyaluronate	glycosaminoglycans	Intraarticular injection, dermal	Hyalgan/ Ialugen Plus	
→ Pancreatin <sup>1)</sup>	Amylase, protease and lipase, prepared from mammalian pancreas	Oral	Creon/Creon Forte/Pancrease/Panzytrat	
Pancreatin/aspergillus Asparaginase	Protease, lipase and cellulose	Oral	Combizym	
	Enzyme from <i>E. coli</i>	Injection IM, IV	Kidrolase Paronal	
Crisantaspase	Asparaginase from <i>Erwinia chrysanthemi</i>	IM, SC, IV	Erwinase	
Anti T-lymphocyte immunoglobulin for human use, animal <sup>2)</sup>	Animal antiserum (from a.o. rabbit, horse)	IV	ATG Fresenius, Thymoglobulin, Lymphoglobulin	

Active ingredient	Type of substance, source	Administration route	Trade names (not exhaustive)	EU-procedure number
Polyclonal sheep anti-digoxin	Animal antiserum	IV infusion	Digitalis antidot	
Hu IFN-alfaLe	Native interferon alfa produced through viral stimulation of leucocytes	Injection SC	Multiferon	
Insulin bovine <sup>1)</sup>	Bovine pancreas	SC, (IM, IV)		UK/H/430
Insulin porcine <sup>1)</sup>	Porcine pancreas	SC, (IM, IV)		
Pepsin powder <sup>1),3)</sup>	Bovine/porcine pancreas			
Trypsin <sup>1)</sup>	Bovine/porcine pancreas			
Chymotrypsin <sup>1)</sup>	Bovine/porcine pancreas			
Glucagon <sup>4)</sup>	Bovine/porcine pancreas	SC, (IM, IV)		
<i>Escherichia coli</i> (Nissle 1917)	strain of <i>Escherichia coli</i> (NISSLE 1917) in viable form	oral	MUTAFLOR, MUTAFLOR mite	
Lysatum bacteriale OM 85 cryodesiccatum	lysatum bacteriale mixtum ( <i>Haemophilus influenzae</i> , <i>Diplococcus pneumoniae</i> , <i>Klebsiella pneumoniae et ozenae</i> , <i>Staphylococcus aureus</i> , <i>Streptococcus pyogenes et viridans</i> , <i>Neisseria catarrhalis</i> )	oral	BRONCHO-VAXOM PRO ADULTIS BRONCHO-VAXOM PRO INFANTIBUS	
OM-89 cryodesiccatum	Lysatum <i>E. coli</i> cryodesiccatum	oral	URO-VAXOM	
Lysatum bacteriale mixtum	<i>Lactobacillus acidophilus</i> , <i>Lactobacillus helveticus</i> , <i>Lactobacillus lactis</i> , <i>Lactobacillus fermentatum</i> , <i>Streptococcus pyogenes A</i> , <i>Enterococcus faecium</i> , <i>Enterococcus faecalis</i> , <i>Streptococcus sanguis</i> , <i>Staphylococcus aureus</i> , <i>Klebsiella pneumoniae</i> , <i>Corynebacterium pseudodiphtheriticum</i> , <i>Fusobacterium (Fusiformis) nucleatum 5,00 mg</i> , <i>Candida albicans</i>	oral	IMUDON	

Active ingredient	Type of substance, source	Administration route	Trade names (not exhaustive)	EU-procedure number
Lysatum bacteriale mixtum	<i>Streptococcus pneumoniae</i> typ I; <i>Streptococcus pneumoniae</i> typ II; <i>Streptococcus pneumoniae</i> typ III; <i>Streptococcus pneumoniae</i> typ V; <i>Streptococcus pneumoniae</i> typ VIII; <i>Streptococcus pneumoniae</i> typ XII; <i>Streptococcus pyogenes</i> A; <i>Streptococcus dysgalactiae</i> C; <i>Enterococcus faecium</i> ; <i>Enterococcus faecalis</i> ; <i>Streptococcus G</i> ; <i>Staphylococcus aureus</i> ; <i>Haemophilus influenzae</i> typ B; <i>Moraxella catarrhalis</i> ; <i>Neisseria subflava flava</i> var.; <i>Neisseria subflava perflava</i> var.; <i>Klebsiella pneumoniae</i> ss <i>pneumoniae</i> ; <i>Acinetobacter calcoaceticus</i> <i>baumanii</i> var.	Nasal spray	IRS 19	
Lactobacillus acidophilus lyophilisatus		Vaginal capsule	GYNOFLOR	
Lactobacillus rhamnosus, Lactobacillus delbrueckii subsp. Bulgaricus, Streptococcus salivarius subsp. termophilus		Vaginal capsule	FERMALAC VAGINAL	
Lysatum bacteriale mixtum	<i>Staphylococcus aureus</i> , <i>Streptococcus mitis</i> , <i>Streptococcus pneumoniae</i> , <i>Streptococcus pyogenes</i> , <i>Klebsiella pneumoniae</i> , <i>Branhamella catarrhalis</i> , <i>Haemophilus influenzae</i>	oral	LUIVAC	

Active ingredient	Type of substance, source	Administration route	Trade names (not exhaustive)	EU-procedure number
Lactobacillus acidophilus, Lactobacillus rhamnosus	<i>Lactobacillus acidophilus</i> , <i>Lactobacillus rhamnosus</i>	oral	LACIDOFIL	
Escherichia coli O83 : K 24 : H 31 lyophilisatum	<i>Escherichia coli</i> O83 : K 24 : H 31	oral	COLINFANT NEW BORN	
Glycoproteini Klebsiella pneumoniae extractum	highly purified glycoproteins (P1 and F1) from the strain of <i>Klebsiella pneumoniae</i>	oral	BIOSTIM	
Phagi particulae contra Staphylococcus polyvalens	antistaphylococcus lysate from phagi	oral	STAFAL	
Lactobacillus acidophilus	<i>Lactobacillus rhamnosus</i> (3 strains), <i>Lactobacillus vaginalis</i> (3 strains), <i>Lactobacillus salivarius</i> (1 strain), <i>Lactobacillus fermentum</i> (1 strain)	Injection IM	SOLCOTRICHOVAC	
Thymostimulin (calf)	Polypeptide immunostimulant factor extracted from calf thymus	---	---	
Calf blood low molecular weight portion	A low molecular fraction of calf blood	eye gel, mouth paste	Solcoseryl	
cerebrolysin	A low molecular fraction of polypeptides extracted from porcine brain	Injection IM, IV	Cerebrolysin	
Phospholipids bovine/porcine	A low molecular fraction of phospholipids extracted from bovine lung	Oral, Endotracheopulmonal surfactant	Essentiale forte/ Survanta/ Curosurf	
Collagenase	Proteolytic enzyme from Clostridium culture	dermal	Iruxol mono	
Deoxyribo-nuclease	Enzyme from beef pancreas	Dermal, solution for inhalation	Pulmozyme/Fibrolan	
Fibrinolysine bovine	enzyme from bovine plasma	dermal	Fibrolan	

Active ingredient	Type of substance, source	Administration route	Trade names (not exhaustive)	EU-procedure number
collagen	Protein from mammalian connective tissue	---	----	
Porcine transfer factor	A low molecular fraction of porcine blood leucocytes	oral	Imunor	
Ribosomes of <i>Klebsiella pneumoniae</i> , <i>Haemophilus influenzae A</i> , <i>Streptococcus pyogenes</i> group A and <i>Streptococcus pneumoniae</i>  Membrane proteoglycans <i>Klebsiella pneumoniae</i>	Desintegrated cells of microorganisms	oral	Ribomunyl	

<sup>1)</sup> Ph. Eur monograph of drug substance available

<sup>2)</sup> Ph. Eur monograph of drug product available

<sup>3)</sup> Pepsin powder PhEur is prepared from gastric mucosa of pigs, cattle or sheep- Pancreas is not indicated as source

<sup>4)</sup> The monograph for animal sourced glucagon has been deleted in 2006