CHANGE REQUEST FORM

Change Request No.: OPS-23-009

Section 1) Description of Change

Type of Change: Temporary / Permanent (please circle as appropriate)

Lonza / Capsugel's safety ~~statemen~~ statement on BSE/TSE has been updated. Refer to attachments 1 & 2.

Change Request Leader (Name)	Jonas Makaster
Change Request Leader Signature	Date: 02 Mar 23

CHANGE REQUEST FORM

Change Request No.: OPS- 33 009

Section 2) Risk Assessment

RAN Reference (if applicable):

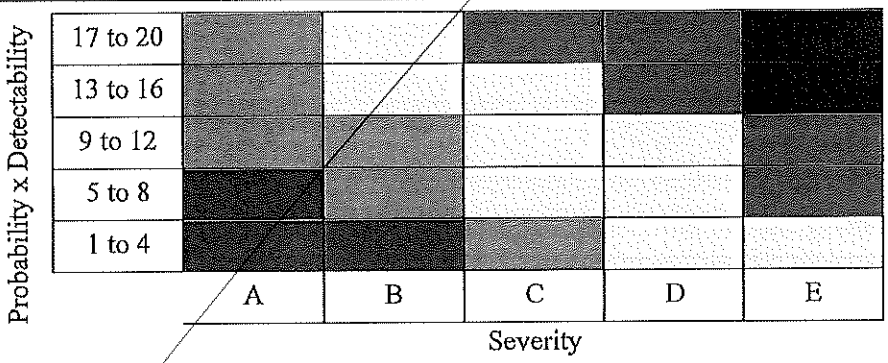
Justification of Risk Level Assigned

Assigned Severity: _____

Assigned Probability: _____

Refer Attachment 1

Assigned Detectability: _____



Key;

	Indicates assessed as a NEGLIGIBLE RISK
	Indicates assessed as a MINOR RISK
	Indicates assessed as a MODERATE RISK.
	Indicates assessed as a MAJOR RISK
	Indicates assessed as a SEVERE RISK

Initial Risk to Quality (Ops) / Safety (Med) Assessment: Negligible Risk ☐ Minor Risk ☐
(please tick one) Moderate Risk ☐ Major Risk ☐ Severe Risk ☐

Signed: Date:

CHANGE REQUEST FORM

Change Request No.: OPS-23-009

Section 3) Change Impact Assessment

Area of Assessment	Change Impact Assessment	Action Required? (Yes/No)	Action No.
Production / Processing			
Products			
Validation / Qualification			
QC Testing / Stability			
Equipment Control			
Material Control	Refer to attachment 1		
Regulatory (CMC Only)			
Regulatory (Other)			
Pharmacovigilance			
Document Control / Site Master File			
Specifications (Including Regulatory Specifications)			
Data Integrity			
Training			

CHANGE REQUEST FORM

Change Request No.: CRS-23-009

Area of Assessment (Continued)	Change Impact Assessment	Action Required? (Yes/No)	Action No.
Buildings and Facilities			
QA Release	Refer to attachment 1		
Qualified Persons			
Other (e.g. MAH representative)			

CHANGE REQUEST FORM

Change Request No.: CRS-22-009

Section 4) Change Request Actions / Deliverables

Action No.	Description of Action / Deliverable	Proposed Completion Date	By Department	Date Action Completed	Verified by (Initials and Date)	Attachment No. Reference (if applicable)	Comments
1							
2				Refer Attachment 1			
3							
4							

CHANGE REQUEST FORM

Change Request No.: 08-23-009

Section 4) Change Request Actions / Deliverables Continued

Action No.	Description of Action / Deliverable	Proposed Completion Date	By Department	Date Action Completed	Verified by (Initials and Date)	Attachment No. Reference (if applicable)	Comments
5							
6				Refer to attachment 1			
7							
8							

CHANGE REQUEST FORM

Change Request No.: OPS-23-009

Section 5) Preapproval Review

Position Title	Reviewer (Tick as Required)	Name	Signature	Date
Pharmacovigilance Representative				
IT Representative				
Automation and Computerised Systems Validation Engineer				
Production Manager (or delegate)	✓	L. Rad		13MAR23
QC Supervisor (or delegate)	✓	D. Ansiè		08Mar23
Senior Product and Technical Services Specialist (or delegate)	✓	C. FLODIN		08Mar23
QA Manager (or delegate)	✓	A. Dooley		07Mar23
Head of Medical and Regulatory Affairs (or delegate)	✓	K. MORGAN		07 MAR 2023
Operations Manager (or delegate)	✓	D. Baird		15Mar 23
Head of Quality (or delegate)	✓	E. Vaicius		11/Mar/23

Any external signatures for preapproval received on FM-451 (refer to Attachment(s) A-F)

Change Request Level: Level 1 ☐; Level 2 ☐; Level 3 ☑; Change Not Approved ☐ (please tick)

Authorisation signature and date: 09 Jun 2022

CHANGE REQUEST FORM

Change Request No.: OPS-23-009

Section 6) Modifications / Changes to Proposed Change Request	
Change Request Leader Signature	Date:

Preapproval of Modifications / Changes (as per pre-approval list)

Position Title	Name	Signature	Date
Production Manager (or delegate)			
QC Supervisor (or delegate)	NM (on 30 Jun 22		
Senior Product and Technical Services Specialist (or delegate)			
QA Manager (or delegate)			
Head of Medical and Regulatory Affairs (or delegate)			
Operations Manager (or delegate)			
Head of Quality (or delegate)			

Any external signatures for preapproval received on FM-451 (refer to Attachment(s) _____)
Comments:

CHANGE REQUEST FORM

Change Request No.: OPS-23-009

Section 7) Change Completion		
Change Completed Successfully: Yes ☑; No ☐. (please tick) Comment N/A		
Further Actions Required: Yes ☐; No ☑. (please tick) Comment N/A		
Change Request Leader Signature	[signature]	Date: 30 Jan 24

Section 8) Effectiveness Check of Change(s)		
Required: Yes ☐; No ☑. (please tick)	Refer to Attachment No.(s): N/A	
Target Completion Date: N/A		
Change Request Leader (or Delegate) Signature	[signature]	Date: 30 Jan 24

CHANGE REQUEST FORM

Change Request No.: DCS-23-009

Section 9) Final Approval for Change Completion

Position Title	Reviewer (Tick as Required)	Name	Signature	Date
Pharmacovigilance Representative				
IT Representative				
Automation and Computerised Systems Validation Engineer				
Production Manager (or delegate)	✓			
QC Supervisor (or delegate)	✓			
Senior Product and Technical Services Specialist (or delegate)	✓	C. FLODIN	C. Flodin	20Feb24
QA Manager (or delegate)	✓	A. Dooley		01Feb24
Head of Medical and Regulatory Affairs (or delegate)	✓			
Operations Manager (or delegate)	✓			
Head of Quality (or delegate)	✓			

Comments:

CHANGE REQUEST FORM

Change Request No.: OPS-23-009

Section 10) Completion of Effectiveness Check
Effectiveness of Change(s) Deemed Acceptable: Yes ☐; No ☐; N/A ☐. (please tick) Refer to Attachment No.(s): _____
Further Actions Required?: Yes ☐; No ☐; (please tick) If yes through CAR / CR No. _____
Verified by: _____ Date: _____

Section 10) Change Close-out
QA Manager: _____ Date Closed: _____
Verified By Head of Quality: _____ Date: _____

Section 3) Change Impact Assessment

Area of Assessment	Change Impact Assessment	Action Required? (Yes/No)	Action No.
Production / Processing	No impact	No	N/A
Products	Refer to Regulatory section.	N/A	N/A
Validation / Qualification	No impact.	No	N/A
QC Testing / Stability	No impact	No	N/A
Equipment Control	No impact	No	N/A
Material Control	Impact release of incoming capsules – refer to specifications.	N/A	N/A
Regulatory (CMC Only)	See Reg impact form MEDFM-127	YES	2,3
Regulatory (Other)	Perform Regulatory Impact assessment as per MEDFM-127-02. Submit Regulatory variations for US and EU markets for Aridol/Osmohale, Bronchitol, PXS5505 & PXS4728 products.	Yes	2, 3
Pharmacovigilance	No impact	No	N/A
Document Control / Site Master File	~~N/A~~ Action required / CF 08Mar23 Update ED-21-011-01 with updated TSE/BSE Statement	~~N/A~~ CF 08Mar23 Yes	~~N/A~~ CF 08Mar23 6
Specifications (Including Regulatory Specifications)	Update the following SP's SP-378-09, SP-087-13, SP-081-13, SP-085-11, SP-083-12, SP-926-03, SP-928-03, SP-925-04, SP-983-01, SP-597-06. Remove C of A requirement relating to *US FDA - 21 CFR Parts 211, 226, 300, 500, 530, 600, 895, and 1271 related to Use of Material Derived from Cattle in Medicinal Products*	Yes	1
Data Integrity	No impact	N/A	N/A
Training	Training requirement: notification of change read record (FM-090) for trained QA personnel that performs release.	Yes	4

08 mar 23

Area of Assessment (Continued)	Change Impact Assessment	Action Required? (Yes/No)	Action No.
Buildings and Facilities			
QA Release	No impact – release will be performed in accordance with updated specifications.	No	N/A
Qualified Persons	Notify QP of change.	Yes	
Other (e.g. MAH representative)	See Attachment 6 for details	YES	2, 5

Oct 23

Section 4) Change Request Actions / Deliverables

Action No.	Description of Action / Deliverable	Proposed Completion Date	By Department	Date Action Completed	Verified by (Initials and Date)	Attachment No. Reference (if applicable)	Comments
1	Update the following SP's SP-378-09, SP-087-13, SP-081-13, SP-085-11, SP-083-12, SP-926-03, SP-928-03, SP-925-04, SP-983-01, SP-597-06. Remove C of A requirement relating to *US FDA - 21 CFR Parts 211, 226, 300, 500, 530, 600, 895, and 1271 related to Use of Material Derived from Cattle in Medicinal Products*	May23	QA	Authorised 29 Jun 23	JM 04 Jul 23	N/A	Specifications were authorised on 29 Jun 23 & 29 Jun 23. Specifications are effective on 05 Jul 23 & 07 Jul 23. JM 04 Jul 23
2	Perform Regulatory Impact assessment as per MEDFM-127-02. Submit Regulatory variations for US and EU markets for Aridol/Osmohale, Bronchitol, PXS5505 & PXS4728 products.	15 MAR 2023	Reg	07 Mar 23	KD 07 Mar 23	Attachment 4	N/A
3	Receive variation approval for submitted variation sin action 2. (MEDFM-128) KD 07 MAR 23	30 Sept 2023	Reg	30 Jun 24	KD 30 Jan 24	Attachment 6	N/A

06 Mar 23

Attachment 1 to OPS-23-009

4	Completion of FM-090 read notification of change record for QA personnel, for SP updates listed in action 1.	May23	QA	07Jul23	JM 03Nov23	N/A	FM-090 records are filed by Doc Control - verified to have been completed. JM 03Nov23
5	NOTIFICATION OF MAHs (other than PXS)	31 MAY 2023	REG & QA	07Mar23	KD 05Jul23	Att# 8	N/A
6	Update ED-21-011-01 with updated TSE/BSE statement	Apr-23	QA	04Dec23	JM 05Dec23	N/A	Refer to ED-21-011-02
7	Update TE-128-02	Apr23	QA	04 Dec 23	JM 05 Dec 23	N/A	Refer to TE-128-03

06Mar23

Attachment 1 to OPS-23-009

Description of Change:

Lonza/Capsugel's most recent safety statement on BSE (Bovine Spongiform Encephalopathy)/TSE (Transmissible Spongiform Encephalopathy) has been updated, refer to attachment 2 for reference.

Summary of change:

USA;

Withdrawal of FDA guidance reference:

US FDA - 21 CFR Parts 211, 226, 300, 500, 530, 600, 895, and 1271 related to Use of Material Derived from Cattle in Medicinal Products

Addition of;

United States Department of Agriculture (USDA) – 9 CFR 94.23 Importation of Gelatin Derived from Bovines.

EU; — Refer to Attachment 3 for other Countries

2017 error KD 07Mar23

Currently submitted CEP (2021)	Updated as at Oct 2022	Comments
Rousselot R1-CEP 2000-029 Rev 05		No Change
Rousselot R1-CEP 2010-043 Rev 00		No Change
PB Gelatins R1-CEP 2000-045 Rev 03	PB Gelatins R1-CEP 2000-045 Rev 04	New CEP
Gelita Group R1-CEP 2001-424 Rev 03		No change
Sterling Gelatin R1-CEP 2001-211 Rev 01		No Change
Nitta Gelatin R1-CEP 2000-344 Rev 02	Nitta Gelatin R1-CEP 2000-344 Rev 03	New CEP
Nitta Gelatin R1-CEP 2004-247 Rev 00		Discontinued
Nitta Gelatin R1-CEP 2004-320 Rev 00		Discontinued
Nitta Gelatin R1 CEP 2005-217 Rev 00	Nitta Gelatin R1 CEP 2005-217 Rev 02	New CEP
	Pioneer Jellice R1-CEP 2008-048 Rev 00	New CEP

Risk Assessment:

Risk assessment:

Assigned Severity: E, Catastrophic risk assigned based on potential disease vCJD (human variant of mad cow disease), which is considered fatal.

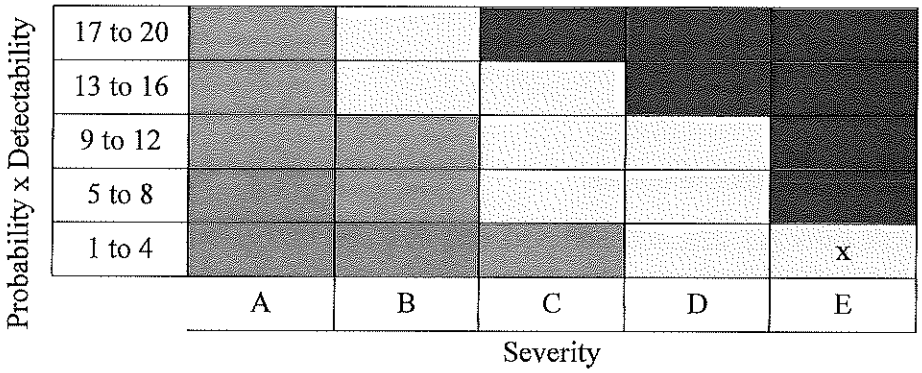
Assigned Probability: 1 Rare – based on low prevalence of the disease.

Assigned Detectability: 2 High – considered high due to current regulations in place.

06Mar23

Attachment 1 to OPS-23-009

Risk: Moderate



	Indicates assessed as a NEGLIGIBLE RISK
	Indicates assessed as a MINOR RISK
	Indicates assessed as a MODERATE RISK.
	Indicates assessed as a MAJOR RISK
	Indicates assessed as a SEVERE RISK

Attachment 2 to 013-23-009

JM 06mar23

Enabling a Healthier World

Lonza
Capsules & Health Ingredients

Statement on TSE/BSE safety

Capsugel® empty gelatin based capsule products

Lonza can use blends of several pharmaceutical gelatins of bovine and/or porcine origin, in full compliance with all applicable pharmaceutical and/or food regulatory statutes.

Related to the specific regulations aiming to secure the TSE/BSE safety, Lonza sources bovine gelatin fully complying with the following:

Europe:

- Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3), which is published by the European Commission following Commission Directive 2003/63/EC, (amending Directive 2001/83/EC on the Community code relating to medicinal products for human use), Annex I, Part I, paragraph 3.2.2.4. Control of excipients.
  These Directives require that applicants for Marketing Authorization must demonstrate that medicinal products are manufactured in accordance with the latest version of this Note for Guidance and compliance is demonstrated by the "Certificate of Suitability" issued to the manufacturer of the bovine gelatin by the European Directorate for the Quality of Medicines (EDQM). As such, **from February 1st 2023**, Lonza manufactures capsules under any (or all) of the following Certificates of Suitability:

  - Rousselot R1-CEP 2000-029-Rev 05
  - Rousselot R1-CEP-2010-043-Rev 00
  - Tessenderlo Group R1-CEP 2000-045-Rev 04
  - Gelita Group R1-CEP 2001-424-Rev 03
  - Sterling Gelatin R1-CEP 2001-211-Rev 01
  - Nitta Gelatin R1-CEP 2000-344-Rev 03
  - Nitta Gelatin R1-CEP 2005-217-Rev 02
  - Pioneer Jellice R1-CEP 2008-048-Rev 00

- Regulation (EC) No 853/2004 laying down specific hygiene rules for food of animal origin.
- Regulation (EC) No 999/2001 laying down rules for the prevention, control and eradication of certain transmissible spongiform encephalopathies.

US:

- United States Food and Drug Administration - 21 CFR Part 189 – "Substances Prohibited from Use in Human Food: Prohibited Cattle Materials."
- United States Department of Agriculture (USDA) – 9 CFR 94.23 Importation of Gelatin Derived from Bovines.

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F +32 3 889 26 22

535 North Emerald Road
Greenwood, SC 29646 USA
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1030A
Puebla 72270, México
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Lonza

Capsules & Health Ingredients

Japan:

- Japanese Ministry of Health, Labor Welfare (MHLW) - "Food Sanitation Law", Chapter 2, Article 7 and Article 10 "Specifications and Standards for Food or additives" revised and announced by MHLW Notice No.0327-2 of March 27, 2015.
- Japanese Ministry of Health, Labor and Welfare - Notification No. 210 of the MHLW issued on May 20, 2003 and the latest version by Notification No. 1002-27 about the partial amendment of the criteria eliminating source country restrictions, applicable from November 25th 2014.

The bovine bone starting material is derived from healthy animals that were slaughtered in a slaughterhouse and that passed an ante-mortem and post-mortem inspection by an official veterinarian.

For what concerns specified risk materials (SRMs), next to the removal of skulls and spinal cords, Lonza's bovine bone gelatin suppliers certify vertebrae removal independent from the geographical origin and/or age of the animals.

Lonza continuously monitors all regulatory activities; please let us know if there are further questions or clarification needed.

Revision History:

Last Update	***Update***
September 2015	Actualization of list of applicable CEPs and legislative references
November 2016	Actualization of US Interim Final Rule to Final Rule
July 2017	Introduction R1-CEP-2010-043 and discontinuation R1-CEP 2001-332, R1-CEP 2003-172, R1-CEP 2000-027 and R1-CEP 2002-110 as from October 1st, 2017
June 2019	Update of R1-CEP-2000-045 from Rev03 to Rev04, Update from R1-CEP-2005-217 from Rev00 to Rev01. Discontinuation of R1-CEP-2004-247 and R1-CEP-2004-320
July 2019	Update of R1-CEP-2005-217 from Rev01 to Rev02
October 2019	Update of R1-CEP 2000-344 from Rev02 to Rev03
January 2020	New LONZA template
September 2021	CEPs in attachment replaced by recently signed versions
October 2022	Introduction R1-CEP 2008-048-Rev 00 Update of regulatory references for the United States

For further information, please contact your Account Solutions Representative.

Last update: October, 2022

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edqm
European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé
COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

Certification of Substances Division

Certificate of suitability
No. R1-CEP 2000-029-Rev 05

Name of the substance:
GELATIN
Limed bone gelatin

Name of holder:
ROUSSELOT
Kanaaldijk Noord 20-21
The Netherlands-5691 NM Son

Site(s) of production:
ROUSSELOT SAS
Chemin Moulins Premiers
France-84800 Isle-Sur-La-Sorgue

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R1-CEP 2000-029-REV 04

After examination of the information provided on the origin of raw material(s) and type of tissue(s) used and on the manufacturing process for this substance on the site(s) of production mentioned above, we certify that the substance **GELATIN** meets the criteria described in the current version of the monograph Products with risk of transmitting agents of animal spongiform encephalopathies no. 1483 of the European Pharmacopoeia, current edition including supplements.

- Country(ies) of origin of source materials:
  Argentina, Australia, Austria, Belgium, Bulgaria, Canada, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, India, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Mexico, the Netherlands, New Zealand, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, United Kingdom and United States of America.

- Nature of animal tissues used in manufacture:
  For Australia, New Zealand, India and Argentina: bovine bones free from skulls and spinal cord but not free from vertebrae
  For all other countries: bovine bones free from skulls and spinal cord for cattle of all age and free from vertebrae for animals of 30 months and over.

- Manufacturing process:
  Alkaline process

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance, or that may alter the risk of transmitting animal spongiform encephalopathy agents.

Address: 7 Allée Kastner, CS 30026
F-67081 Strasbourg (France)
Tel: +33 (0) 3 88 41 30 30 – Fax: +33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet: http://www.edqm.eu

35 Manufacture of the substance shall take place in accordance with a suitable quality assurance
36 system, and in accordance with the dossier submitted.

37 Failure to comply with these provisions will render this certificate void.

38 The certificate is valid provided that there has been no deterioration in the TSE status of the
39 country(ies) of origin of the source material.

40 This certificate is renewed from **15 May 2005** according to the provisions of
41 Resolution AP-CSP (07) 1, and of Directive 2001/83/EC and Directive 2001/82/EC and any
42 subsequent amendment, and the related guidelines.

43 This certificate has:
44 lines.

On behalf of the
Director of EDQM

Strasbourg, 18 July 2014

DECLARATION OF ACCESS *(to be filled in by the certificate holder under their own responsibility)*

ROUSSELOT, as holder of the certificate of suitability

R1-CEP 2000-029-Rev 05 for Gelatin

hereby authorises Any pharmaceutical company .....
(*name of the pharmaceutical company*)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): (*name of product(s) and marketing number(s), if known*)

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been made since the granting of this version of the certificate.

Date and Signature (*of the CEP holder*):
24 August 2021

Kathleen Jacobs
Global Regulatory Director
Rousselot BV
Meulestedekaai 81
B-9000 Gent

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F-67081 Strasbourg (France)
Tel: +33 (0) 3 88 41 30 30 – Fax: +33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet: http://www.edqm.eu

COUNCIL OF EUROPE

CONSEIL DE L'EUROPE

Certification of Substances Division

Certificate of suitability
No. R1-CEP 2010-043-Rev 00

Name of the substance:
GELATIN
Limed bone gelatin

Name of holder:
ROUSSELOT
Kanaaldijk Noord 20-21
The Netherlands-5691 NM Son

Site(s) of production:
ROUSSELOT PEABODY INC.
227 Washington Street
United States Am.-01960 Peabody, Massachusetts

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R0-CEP 2010-043-REV 02

After examination of the information provided on the origin of raw material(s) and type of tissue(s) used and on the manufacturing process for this substance on the site(s) of production mentioned above, we certify that the substance **GELATIN** meets the criteria described in the current version of the monograph Products with risk of transmitting agents of animal spongiform encephalopathies no. 1483 of the European Pharmacopoeia, current edition including supplements.

- Country(ies) of origin of source materials :
  Canada, United States of America and India

- Nature of animal tissues used in manufacture:
  Bovine bones free from skulls and spinal cord, and free from vertebrae for animals over 30 months: Canada and United States of America.
  Bovine bones free from skulls and spinal cord but not free from vertebrae: India

- Manufacturing process:
  Alkaline process

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance, or that may alter the risk of transmitting animal spongiform encephalopathy agents.

Address: 7 Allée Kastner, CS 30026
F-67081 Strasbourg (France)
Tel: +33 (0) 3 88 41 30 30 – Fax: +33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet: http://www.edqm.eu

Manufacture of the substance shall take place in accordance with a suitable quality assurance system, and in accordance with the dossier submitted.

Failure to comply with these provisions will render this certificate void.

The certificate is valid provided that there has been no deterioration in the TSE status of the country(ies) of origin of the source material.

This certificate is renewed from **5 January 2016** according to the provisions of Resolution AP-CSP (07) 1, and of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment, and the related guidelines.

This certificate has:
lines.

On behalf of the
Director of EDQM

Strasbourg, 10 December 2015

DECLARATION OF ACCESS *(to be filled in by the certificate holder under their own responsibility)*

ROUSSELOT, as holder of the certificate of suitability

R1-CEP 2010-043-Rev 00 for Gelatin

hereby authorises Any pharmaceutical company
(*name of the pharmaceutical company*)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): (*name of product(s) and marketing number(s), if known*)

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been made since the granting of this version of the certificate.

Date and Signature (*of the CEP holder*):
24 August 2021

Kathleen Jacobs
Global Regulatory Director
Rousselot BV
Meulestedekaai 81
B-9000 Gent

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Internet: http://www.edqm.eu

European Directorate for the Quality of Medicines & HealthCare
Direction européenne de la qualité du médicament & soins de santé
COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

Certification of Substances Department

Certificate of suitability
No. R1-CEP 2000-045-Rev 04

Name of the substance:
GELATIN
Limed bone gelatin

Name of holder:
TESSENDERLO GROUP N.V.
Division PB Leiner
Marius Duchéstraat 260
Belgium-1800 Vilvoorde

Site(s) of production:
PB GELATINS GMBH
Grosse Drakenburgerstrasse 43
Germany-31582 Nienburg

PB GELATINS UK LTD
Treforest, Industrial Estate,Pontypridd
United Kingdom-CF37 5SQ Rhondda Cynon TAFF

TESSENDERLO GROUP N.V.
Division PB Leiner
Marius Duchéstraat 260
Belgium-1800 Vilvoorde

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R1-CEP 2000-045-REV 03

After examination of the information provided on the origin of raw material(s) and type of tissue(s) used and on the manufacturing process for this substance on the site(s) of production mentioned above, we certify that the substance **GELATIN** meets the criteria described in the current version of the monograph Products with risk of transmitting agents of animal spongiform encephalopathies no. 1483 of the European Pharmacopoeia, current edition including supplements.

- Country(ies) of origin of source materials:
  Austria, Belgium, Bulgaria, Canada, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, India, Ireland, Italy, Latvia, Lithuania, Luxemburg, Malta, The Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, United Kingdom and United States of America.
- Nature of animal tissues used in manufacture:
  Bovine bones free from skulls and spinal cord, and free from vertebrae for animals of 30 months and over: Austria, Belgium, Bulgaria, Canada, Croatia, Cyprus, Czech Republic,

Address: 7 Allée Kastner, CS 30026
F-67081 Strasbourg (France)
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Internet: http://www.edqm.eu

Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxemburg, Malta, The Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland and United Kingdom.
Bovine bones free from skulls and spinal cord: United States of America and India.

- Manufacturing process: Alkaline process

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance, or that may alter the risk of transmitting animal spongiform encephalopathy agents.

Manufacture of the substance shall take place in accordance with a suitable quality assurance system, and in accordance with the dossier submitted.

Failure to comply with these provisions will render this certificate void.

The certificate is valid provided that there has been no deterioration in the TSE status of the country(ies) of origin of the source material.

This certificate is renewed from **18 July 2005** according to the provisions of Resolution AP-CSP (07) 1, and of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment, and the related guidelines.

This certificate has:
lines.

On behalf of the
Director of EDQM

Strasbourg, 29 April 2019

DECLARATION OF ACCESS *(to be filled in by the certificate holder under their own responsibility)*

TESSENDERLO GROUP N.V., as holder of the certificate of suitability

R1-CEP 2000-045-Rev 04 for Gelatin

hereby authorises .....A.N.Y...P.H.A.R.M.A.C.E.U.T.I.C.A.L...C.O.M.P.A.N.Y.....
(name of the pharmaceutical company)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): (*name of product(s) and marketing number(s), if known*)

Products containing gelatin supplied by PB Leiner

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been made since the granting of this version of the certificate.

Date and Signature (*of the CEP holder*):

24/08/2021

Dominique ROLIN
Regulatory Leader

TESSENDERLO GROUP N.V.
att. PB Leiner
Marius Duchestraat 260
B-1800 VILVOORDE

Address: 7 Allée Kastner, CS 30026
F-67081 Strasbourg (France)
Tel: +33 (0) 3 88 41 30 30 – Fax: +33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet: http://www.edqm.eu

Certificate of suitability
No. R1-CEP 2001-424-Rev 03

Name of the substance:
GELATIN
Limed bone gelatin - Very short limed bone gelatin

Name of holder:
GELITA GROUP
Uferstrasse 7
Germany-69412 Eberbach

Site(s) of production:
GELITA AG
Gammelsbacher Strasse 2
Germany-69412 Eberbach

GELITA AG
Alpenstrasse 44
Germany-87700 Memmingen

GELITA USA INC.
2445 Port Neal Industrial Rd
United States Am.-51054 Sergeant Bluff, Iowa

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R1-CEP 2001-424-REV 02

After examination of the information provided on the origin of raw material(s) and type of tissue(s) used and on the manufacturing process for this substance on the site(s) of production mentioned above, we certify that the substance **GELATIN** meets the criteria described in the current version of the monograph Products with risk of transmitting agents of animal spongiform encephalopathies no. 1483 of the European Pharmacopoeia, current edition including supplements.

- Countries of origin of source materials:
  Austria, Belgium, Brazil, Bulgaria, Canada, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, The Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Switzerland, Sweden, United Kingdom and United States of America

- Nature of animal tissues used in manufacture:
  Bovine bones free from skulls, spinal cord and vertebrae from cattle older than 30 months

- manufacturing process:
  Alkaline process

Address: 7 Allée Kastner, CS 30026
F-67081 Strasbourg (France)
Tel: +33 (0) 3 88 41 30 30 – Fax: +33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet: http://www.edqm.eu

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance, or that may alter the risk of transmitting animal spongiform encephalopathy agents.

Manufacture of the substance shall take place in accordance with a suitable quality assurance system, and in accordance with the dossier submitted.

Failure to comply with these provisions will render this certificate void.

The certificate is valid provided that there has been no deterioration in the TSE status of the country(ies) of origin of the source material.

This certificate is renewed from **11 December 2006** according to the provisions of Resolution AP-CSP (07) 1, and of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment, and the related guidelines.

This certificate has: lines.

On behalf of the
Director of EDQM

Strasbourg, 19 September 2014

DECLARATION OF ACCESS *(to be filled in by the certificate holder under their own responsibility)*

GELITA Group, as holder of the certificate of suitability

R1-CEP 2001-424-Rev 03 for Gelatin

hereby authorises any pharmaceutical company
(*name of the pharmaceutical company*)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): (*name of product(s) and marketing number(s), if known*)

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been made since the granting of this version of the certificate.

GELITA AG
Uferstr. 7
69412 Eberbach

Date and Signature (*of the CEP holder*):
23.08.2021

i.A. Klaus Mathias
Customer Service

i.A. Philipp Sommer
Customer Service

Address: 7 Allée Kastner, CS 30026
F-67081 Strasbourg (France)
Tel: +33 (0) 3 88 41 30 30 – Fax: +33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet: http://www.edqm.eu

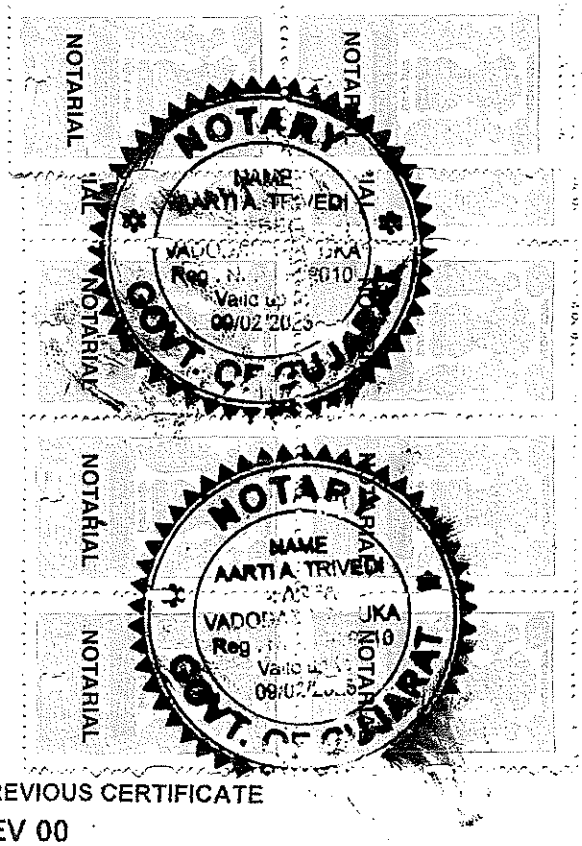
Sr. No. : 6406
Date: 25/08/2021

European Directorate for the
Quality of Medicines & HealthCare

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

Certification of Substances Division

Certificate of suitability
No. R1-CEP 2001-211-Rev 01



Name of the substance:
GELATIN
Limed Bone Gelatin

Name of holder:
STERLING BIOTECH LIMITED
Division - Sterling Gelatin
ECP Road, Village Karakhadi
Taluka Padra
India-391 450 Vadodara, Gujarat

Site(s) of production:
STERLING BIOTECH LIMITED
Division - Sterling Gelatin
ECP Road, Village Karakhadi
Taluka Padra
India-391 450 Vadodara, Gujarat

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R1-CEP 2001-211-REV 00

After examination of the information provided on the origin of raw material(s) and type of tissue(s) used and on the manufacturing process for this substance on the site(s) of production mentioned above, we certify that the substance **GELATIN** meets the criteria described in the current version of the monograph Products with risk of transmitting agents of animal spongiform encephalopathies no. 1483 of the European Pharmacopoeia, current edition including supplements.

– country(ies) of origin of source materials:	India
– nature of animal tissues used in manufacture:	Bovine bones free from skulls, spinal cord and vertebrae
– manufacturing process:	Alkaline process

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance, or that may alter the risk of transmitting animal spongiform encephalopathy agents.

Address: 7, allée Kastner, CS 30026 - F - 67081 Strasbourg (France)
Telephone: 33 (0) 3 88 41 30 30 - Fax: 33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet : http://www.edqm.eu

AFAQ ISO 9001

- Manufacture of the substance shall take place in accordance with a suitable quality assurance system such as ISO 9001 and HACCP standards, and in accordance with the dossier submitted.

Failure to comply with these provisions will render this certificate void.

The certificate is valid provided there has been no deterioration in the TSE status of the country(ies) of origin of the source material.

This certificate is renewed from **17 May 2007** according to the provisions of Resolution AP-CSP (93) 5 as amended, and of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment, and the related guidelines.

This certificate has
lines.

NOTARY AARTI A. TRIVEDI AREA: VADODARA TALUKA REG. No. 1155 2010 GOVT. OF GUJARAT (INDIA)

On behalf of the
Director of EDQM

Strasbourg, November 2010

A.A. Trivedi
ATTESTED
AARTI A. TRIVEDI NOTARY - VADODARA
My Commission Date Exp on 9 Feb 2025
25-08-2021

DECLARATION OF ACCESS *(to be filled in by the certificate holder under their own responsibility)*

STERLING BIOTECH LIMITED, as holder of the certificate of suitability

R1-CEP 2001-211-Rev 01 for GELATIN

hereby authorises Any Pharmaceutical Company
(name of the pharmaceutical company)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): *(name of product(s) and marketing number(s), if known)*

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been made since the granting of this version of the certificate.

Date and Signature *(of the CEP holder)*:

Vikram Kale
Vice President(QC/QA)
Date: 24/08/21

STERLING BIOTECH LIMITED
Divison - Sterling Gelatin
Exp Road, Village : Kankrej-[illegible]
Ta.: Padra, Dist. Vadodara, Gujarat India.

NOTARY NAME AARTI A. TRIVEDI VADODARA TALUKA Reg. No. [illegible]10 Valid up to 09/02/2025 GOVT. OF GUJARAT

Address: 7, allée Kastner, CS 30026 - F - 67081 Strasbourg (France)
Telephone: 33 (0) 3 88 41 30 30 - Fax: 33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet : http://www.edqm.eu

AFAQ ISO 9001

Certification of Substances Department

Certificate of suitability
No. R1-CEP 2000-344-Rev 03

Name of the substance:
GELATIN
Limed Bone Gelatin

Name of holder:
NITTA GELATIN INDIA LTD.
Post Box No. 4262 SBT Avenue
Panampilly Nagar
India-682 036 Cochin, Kerala

Site(s) of production:
NITTA GELATIN INDIA LTD.
Gelatin Division, Post Box No. 3109
Infopark P.O. Kakkanad
India-682 042 Cochin, Kerala

NITTA GELATIN INDIA LTD.
Ossein Division
Kathikudam P.O. Koratty
India-680 308 Trissur, Kerala

NITTA GELATIN INDIA LTD.
Reva Division
Plot No. 832, G.I.D.C. Industrial Estate
India-393 110 Jhagadia, Gujarat

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R1-CEP 2000-344-REV 02

After examination of the information provided on the origin of raw material(s) and type of tissue(s) used and on the manufacturing process for this substance on the site(s) of production mentioned above, we certify that the substance **GELATIN** meets the criteria described in the current version of the monograph Products with risk of transmitting agents of animal spongiform encephalopathies no. 1483 of the European Pharmacopoeia, current edition including supplements.

- Country of origin of source materials:
  India
- Nature of animal tissues used in manufacture:
  Bovine bones free from skulls, spinal cord and vertebrae
- Manufacturing process:
  Alkaline process

Address: 7 Allée Kastner, CS 30026
F-67081 Strasbourg (France)
Tel: +33 (0) 3 88 41 30 30 - Fax: +33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet: http://www.edqm.eu

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance, or that may alter the risk of transmitting animal spongiform encephalopathy agents.

Manufacture of the substance shall take place in accordance with a suitable quality assurance system, and in accordance with the dossier submitted.

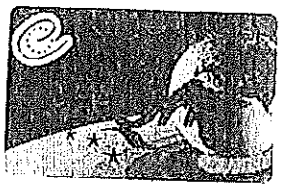
Failure to comply with these provisions will render this certificate void.

The certificate is valid provided that there has been no deterioration in the TSE status of the country(ies) of origin of the source material.

This certificate is renewed from **5 June 2007** according to the provisions of Resolution AP-CSP (07) 1, and of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment, and the related guidelines.

This certificate has:
lines.

On behalf of the
Director of EDQM



Strasbourg, 10 October 2019

DECLARATION OF ACCESS *(to be filled in by the certificate holder under their own responsibility)*

NITTA GELATIN INDIA LTD., as holder of the certificate of suitability

R1-CEP 2000-344-Rev 03 for Gelatin

Any pharmaceutical company

hereby authorises .....
(*name of the pharmaceutical company*)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): (*name of product(s) and marketing number(s), if known*)

Empty Hard Gelatin Capsules

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been made since the granting of this version of the certificate.

For Nitta Gelatin India Limited

Date and Signature (*of the CEP holder*):
25/08/2021

Dr. K.R. Chitra
AGM (QA)

Address: 7 Allée Kastner, CS 30026
F-67081 Strasbourg (France)
Tel: +33 (0) 3 88 41 30 30 - Fax: +33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet: http://www.edqm.eu

Certification of Substances Department

Certificate of suitability
No. R1-CEP 2005-217-Rev 02

Name of the substance:
GELATIN
Limed bone gelatin

Name of holder:
NITTA GELATIN INC.
4-26, Sakuragawa 4-chome
Japan-556-0022 Naniwa-Ku, Osaka

Site(s) of production:
NITTA GELATIN INC.
Osaka Plant
2-22, Futamata
Japan-581-0024 Yao-Shi, Osaka

THAI BONES INDUSTRY CO., LTD.
Ayutthaya Plant
30 Moo 12 Tambol Utai
Thailand-13210 Amphur Uthai, Ayutthaya

THAI BONES INDUSTRY CO., LTD.
Rangsit Plant
27/1 Moo 5, Tambol Klongnueng
Thailand-12120 Amphur Klongluang, Patumthanee

NITTA GELATIN INDIA LTD.
Ossein Division
Kathikudam P.O. Koratty
India-680 308 Trissur, Kerala

NITTA GELATIN INDIA LTD.
Reva Division
Plot No. 832, G.I.D.C. Industrial Estate
India-393 110 Jhagadia

BAMNI PROTEINS LIMITED
P.O. Dudholi, Bamni
Chandrapur District
India-422 701 Via Ballarpur, Maharashtra

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE

R1-CEP 2005-217-REV 01

After examination of the information provided on the origin of raw material(s) and type of tissue(s) used and on the manufacturing process for this substance on the site(s) of production mentioned above, we certify that the substance **GELATIN** meets the criteria described in the current version of the monograph Products with risk of transmitting agents of animal spongiform encephalopathies no. 1483 of the European Pharmacopoeia, current edition including supplements.

- Countries of origin of source materials:
  Argentina, Canada, France, India, New Zealand and United States of America.
- Nature of animal tissues used in manufacture:
  Bovine bones free from skull and spinal cord, free from vertebrae over 30 months of age.

Address: 7 Allée Kastner, CS 30026
F-67081 Strasbourg (France)
Tel: +33 (0) 3 88 41 30 30 – Fax: +33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet: http://www.edqm.eu

– Manufacturing process:
Alkaline process

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance, or that may alter the risk of transmitting animal spongiform encephalopathy agents.

Manufacture of the substance shall take place in accordance with a suitable quality assurance system, and in accordance with the dossier submitted.

Failure to comply with these provisions will render this certificate void.

The certificate is valid provided that there has been no deterioration in the TSE status of the country(ies) of origin of the source material.

This certificate is renewed from **30 March 2011** according to the provisions of Resolution AP-CSP (07) 1, and of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment, and the related guidelines.

This certificate has:
lines.

On behalf of the
Director of EDQM

Strasbourg, 16 July 2019

DECLARATION OF ACCESS *(to be filled in by the certificate holder under their own responsibility)*

Nitta Gelatin Inc., as holder of the certificate of suitability

R1-CEP 2005-217-Rev 02 for Gelatin

hereby authorises ..... Any Pharmaceutical customer .....
(*name of the pharmaceutical company*)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): (*name of product(s) and marketing number(s), if known*)

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been made since the granting of this version of the certificate.

Date and Signature (*of the CEP holder*):

September 8, 2021 T. Nakatani

Date

Takanori Nakatani
General Manager, Quality Assurance Department
Nitta Gelatin Inc.

Address: 7 Allée Kastner, CS 30026
F-67081 Strasbourg (France)
Tel: +33 (0) 3 88 41 30 30 – Fax: +33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet: http://www.edqm.eu

edqm
European Directorate for the Quality of Medicines & HealthCare

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

Certification of Substances Division

Certificate of suitability
No. R1-CEP 2008-048-Rev 00

Name of the substance:
GELATIN
Limed bone gelatin

Name of holder:
PIONEER JELLICE INDIA PRIVATE LIMITED
Revenue Survey No. 65, 66 & 67, Semman Kuppam
Chidambaram Main Road
India-607 005 Cuddalore

Site(s) of production:
PIONEER JELLICE INDIA PRIVATE LIMITED
Revenue Survey No. 65, 66 & 67, Semman Kuppam
Chidambaram Main Road
India-607 005 Cuddalore

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R0-CEP 2008-048-REV 00

After examination of the information provided on the origin of raw material(s) and type of tissue(s) used and on the manufacturing process for this substance on the site(s) of production mentioned above, we certify that the substance **GELATIN** meets the criteria described in the current version of the monograph Products with risk of transmitting agents of animal spongiform encephalopathies no. 1483 of the European Pharmacopoeia, current edition including supplements.

- Country of origin of source materials:
  India

- Nature of animal tissues used in manufacture:
  Bovine bones free from skulls and vertebrae

- Manufacturing process:
  Alkaline process

Address: 7 Allée Kastner, CS 30026
F-67081 Strasbourg (France)
Tel: +33 (0) 3 88 41 30 30 – Fax: +33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet: http://www.edqm.eu

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance, or that may alter the risk of transmitting animal spongiform encephalopathy agents.

Manufacture of the substance shall take place in accordance with a suitable quality assurance system, and in accordance with the dossier submitted.

Failure to comply with these provisions will render this certificate void.

The certificate is valid provided that there has been no deterioration in the TSE status of the country(ies) of origin of the source material.

This certificate is renewed from **2 February 2014** according to the provisions of Resolution AP-CSP (07) 1, and of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment, and the related guidelines.

This certificate has:
lines.

On behalf of the
Director of EDQM

Strasbourg, 30 January 2014

DECLARATION OF ACCESS *(to be filled in by the certificate holder under their own responsibility)*

PIONEER JELLICE INDIA PRIVATE LIMITED, as holder of the certificate of suitability

R1-CEP 2008-048-Rev 00 for Gelatin

hereby authorises ANY PHARMACEUTICAL COMPANY
(name of the pharmaceutical company)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): (*name of product(s) and marketing number(s), if known*)

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been made since the granting of this version of the certificate.

Date and Signature (*of the CEP holder*): 23rd Aug 2022

T. Arumugam
Vice President
Pioneer Jellice India Private Limited

PIONEER JELLICE INDIA PRIVATE LIMITED CUDDALORE

Address: 7 Allée Kastner, CS 30026
F-67081 Strasbourg (France)
Tel: +33 (0) 3 88 41 30 30 – Fax: +33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet: http://www.edqm.eu

Up-to-date CEPs of Bronchitol EU (EMA)

Currently submitted CEP (2017)	Updated as at Oct 2022	Comments
Rousselot R1-CEP 2000-029 Rev 05		No Change
Rousselot R1-CEP 2010-043 Rev 00		No Change
PB Gelatins R1-CEP 2000-045 Rev 03	PB Gelatins R1-CEP 2000-045 Rev 04	New CEP
Gelita Group R1-CEP 2001-424 Rev 03		No change
Sterling Gelatin R1-CEP 2001-211 Rev 01		No Change
Nitta Gelatin R1-CEP 2000-344 Rev 02	Nitta Gelatin R1-CEP 2000-344 Rev 03	New CEP
Nitta Gelatin R1-CEP 2004-247 Rev 00		Discontinued
Nitta Gelatin R1-CEP 2004-320 Rev 00		Discontinued
Nitta Gelatin R1 CEP 2005-217 Rev 00	Nitta Gelatin R1 CEP 2005-217 Rev 02	New CEP
	Pioneer Jellice R1-CEP 2008-048 Rev 00	New CEP

Up-to-date CEPs of Bronchitol Switzerland, Bronchitol-Pharmaxis Russia/ Bronchitol-GEN Kazakhstan/ Bronchitol-Pharmaxis Uzbekistan (CIS) and Aridol Australia, UK/Korea/Taiwan PXS-5505, Bronchitol MHRA

Currently submitted CEP V. 2019	Updated as at CEP V. 2022	Comments
Rousselot R1-CEP 2000-029 Rev 05		No Change
Rousselot R1-CEP 2010-043 Rev 00		No Change
Tessenderlo Group R1-CEP 2000-045 Rev 04		No Change
Gelita Group R1-CEP 2001-424 Rev 03		No change
Sterling Gelatin R1-CEP 2001-211 Rev 01		No Change
Nitta Gelatin R1-CEP 2000-344 Rev 03		No Change
Nitta Gelatin R1 CEP 2005-217 Rev 02		No Change
	Pioneer Jellice R1-CEP 2008-048 Rev 00	New CEP

Prepared by K. Dunn KD 07 Mar 23 **Checked by K. Morgan** 7 MAR 2023

Attachment 4 CR - OPS - 23-009 KWL 7 MAR 2023

pharmaxis	MEDFM-127-02	Date Effective: 08-Mar-23	Page 1 of 4

REGULATORY IMPACT FORM FOR PLANNED CHANGES

Attachment 4 to change request number (incl. title of the change request): OPS-23-009

The tables below summarise the full regulatory requirements/actions for the change and a track record for submission, approval and completion. Actions should be noted for both commercial products and products in development. Consideration should also be given to any local requirements in Europe for Marketed products (ie Spain or Italy, where additional local processes are required) and any ongoing clinical trials/INDs etc for products in clinical development. The Regulatory Notification form (MEDFM-128) should be used to track required notifications to PV/Marketing/Partners.

Bronchitol

Market	Affected (Yes/No)	Requirements/Timing/Comments	Submitted	Submission Reference# (Seq#)	Verified (Initial / date)	Date approved by Competent Authority if required	Verified (Initial / date)
Australia	Yes	BTC notified. BTC to submit.	BTC to submit.	N/A	KD 07Mar23	13 Jun 23 ~~N/A~~ Δ	KD 05 Jul 23 ~~N/A~~ Δ
Australia Export Product (AUST L187575)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Europe	Yes	Submit within 3 month - target	14 Aug 23	00115	KD 21~~Aug~~ 23 Aug 23 error KD 21 Aug 23	past 30 days from the 14 Aug 23 Δ	KD 30 Jan 24
MHRA	Yes	Submitted Refer to Att # 9 approval KD 24 Jul 23	22Feb23	0007	KD 07Mar23	21 Jul 23	KD 24 Jul 23
Russia	Yes	Inform MAH	GEN to submit	N/A	KD 07Mar23	N/A	N/A
Brazil	Yes	Inform MAH	United Medical/KnightTX to submit	N/A	KD 07Mar23	N/A	N/A

2x Δ error KD 05 Jul 23

REGULATORY IMPACT FORM FOR PLANNED CHANGES

US	Yes	Inform MAH	Chiesi Inc. to submit	N/A	KD 07Mar23	N/A	N/A
Switzerland	Yes	Submit within 12 month following the Date of Purchase order (not known yet) AHA 11 KD 27Aug23	EffRx to submit	N/A	KD 07Mar23	N/A	N/A
Kazakhstan	Yes	Inform MAH	GEN to submit	N/A	KD 07Mar23	N/A	N/A
Uzbekistan	Yes	Inform MAH	GEN to submit	N/A	KD 07Mar23	N/A	N/A
Azerbaijan	Yes	Inform MAH	GEN to submit	N/A	KD 07Mar23	N/A	N/A

Prepared by: KD 07 Mar 23 **Checked by:** 07 MAR 2023

REGULATORY IMPACT FORM FOR PLANNED CHANGES

Aridol

Market		Affected (Yes/No)	Requirements/Timing/Comments	Submitted	Submission Reference# (Seq#)	Verified (Initial / date)	Date approved by Competent Authority if required	Verified (Initial / date)
Australia		Yes	BTC notified.	BTC to submit	N/A	KD 07Mar23	N/A	N/A
Europe	Sweden	Yes	Not submit. Change controlled through internal GMP procedures.	N/A	N/A	N/A	N/A	N/A
	Denmark	Yes	Not submit. Change controlled through internal GMP procedures.	N/A	N/A	N/A	N/A	N/A
	Ireland	Yes	Not submit. Change controlled through internal GMP procedures.	N/A	N/A	N/A	N/A	N/A
	UK	Yes	Not submit. Change controlled through internal GMP procedures.	N/A	N/A	N/A	N/A	N/A
	Germany	Yes	Not submit. Change controlled through internal GMP procedures.	N/A	N/A	N/A	N/A	N/A
	Norway	Yes	Not submit. Change controlled through internal GMP procedures.	N/A	N/A	N/A	N/A	N/A
	Spain	Yes	Not submit. Change controlled through internal GMP procedures.	N/A	N/A	N/A	N/A	N/A
	Finland	Yes	Not submit. Change controlled through internal GMP procedures.	N/A	N/A	N/A	N/A	N/A
Korea		Yes	Inform MAH	Clinigen to submit	KD 07Mar23	N/A	N/A	N/A
Canada		Yes	No require any variation submission	N/A	N/A	N/A	N/A	N/A
US		Yes	No require any variation submission	N/A	N/A	N/A	N/A	N/A

Prepared by: KD 07 Mar 23 **Checked by:** Kristin Morgan 07 MAR 2023

REGULATORY IMPACT FORM FOR PLANNED CHANGES

INVESTIGATIONAL MEDICINAL PRODUCTS/CLINICAL TRIAL PRODUCTS: PRODUCT NAME PXS- 5505

Market		Affected (Yes/No)	Requirements/Timing/Comments	Submitted	Submission Reference# (Seq#)	Verified (Initial / date)	Date approved by Competent Authority if required	Verified (Initial / date)
Australia		No	No require any variation submission	N/A	N/A	N/A	N/A	N/A
Europe	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
UK		Yes	KM to notify Parexel - MF-101.	N/A for PXS -		KM - not updating dossier at this time KM 26 OCT 2023		
Canada		N/A	N/A	N/A	N/A	N/A	N/A	N/A
US		No	No require any variation submission	N/A	N/A	N/A	N/A	N/A
Singapore		~~Yes~~ N	~~update submit with new protocol~~ ~~MF-101~~ if this goes ahead.			N/A 26 OCT 2023		
Taiwan		NO ~~Yes~~	KM 26/10/2023 " " N/A "			Refer to Attachment 2		
Korea		NO ~~Yes~~	KM 26 OCT 2023 " N/A "				26 OCT 2023	

Prepared by: KM 07 Mar 23 **Checked by:** Kristin Morgan 07 MAR 2023

REGULATORY IMPACT FORM FOR PLANNED CHANGES

INVESTIGATIONAL MEDICINAL PRODUCTS/CLINICAL TRIAL PRODUCTS: PRODUCT NAME PXS- 4728

Market	Affected (Yes/No)	Requirements/Timing/Comments	Submitted	Submission Reference# (Seq#)	Verified (Initial / date)	Date approved by Competent Authority if required	Verified (Initial / date)
Australia	NO	Not requiring any Variation or submission	N/A	N/A	N/A	N/A	N/A
Europe							
UK	YES	Included in IMPD AUG 2023	OCT 2023	ALLUcent submitted to MHRA + to Novotech + PXS			KM 26 OCT 2023

N/A 26 OCT 23

Prepared by: K. MORGAN Kristin Morgan **Checked by:** KM.

Attachment 5 for OPS -23-009 KD 07Mar23

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22nd February 2023

Medicines and Healthcare Products Regulatory Agency (MHRA)
10 South Colonnade
Canary Wharf
London
E14 4PU
UK

Subject:	**Type IA Grouped Variation**
Product:	**Bronchitol 40mg inhalation powder, hard capsules (Mannitol)**
MA number:	**PLGB 50608/0002**
eCTD Sequence:	**0007**

Dear Sir / Madam,

On behalf of the marketing authorisation holder (MAH), namely Pharmaxis Europe Limited, please find enclosed the submission of a Type IA grouped variation for Bronchitol 40mg inhalation powder, hard capsules (Mannitol).

This Type IA grouped variation consists of the following five variations:

- A Type IAIN, Category A.5.a – which serves to report an update to the address of a manufacturing site responsible for batch release of the finished product – namely an update to the address of MIAS Pharma Limited. This update involves no physical move of the site, but is to reflect a local council change to the postal address.
- A Type IA, Category A.7 variation, which serves to delete a manufacturer responsible for batch release / secondary packaging of the finished product – namely to delete Arvato Supply Chain Solutions SE.
- Type IA, Category B.I.a.1.f variation, which serves to report the replacement of one of the manufacturing sites responsible for quality control testing of the active substance - namely to replace the site of Eurofins ams Laboratories Pty Ltd, 8 Rachael Close, Silverwater NSW 2128, Australia with the site of Eurofins ams Laboratories Pty Ltd, 179 Magowar Road, Girraween, NSW 2145, Australia.
- A Type IA, Category B.II.b.2.a variation, which serves to report an update to the address of one of the manufacturing sites responsible for quality control testing of the finished product - namely to replace the site of Eurofins ams Laboratories Pty Ltd, 8 Rachael Close, Silverwater NSW 2128, Australia with the site of Eurofins ams Laboratories Pty Ltd, 179 Magowar Road, Girraween, NSW 2145, Australia.
- A Type IA, Category B.III.1.b.2 variation, which serves to provide a TSE Certificate for an new manufacturer of an excipient – namely to add the TSE CEP for Pioneer Jellice's gelatine [R1-CEP 2008-048-Rev 00] for inclusion in Capsugel's BSE Declaration as displayed in Module 1.2.5.12 and Module 3.2.R.3.2.

This variation sequence (eCTD sequence 0005) is submitted via the MHRA's Submission Portal and contains the following documentation:

Module 1

- Module 1.0 Cover Letter (including sequence tracking table)
- Module 1.2 Variation Application Form
- Module 1.2 Additional – MHRA rejection from previous invalidated Type IA(G) procedure
- Module 1.2 Annex 5.6 - Manufacturer's Authorisation for MIAS Pharma Limited (updated)
- Module 1.2 Annex 5.6 - Manufacturer's Authorisation for Eurofins ams Laboratories Pty Ltd
- Module 1.2 Annex 5.8 - Flow Diagram (updated)
- Module 1.2 Annex 5.9 - GMP Certificate for MIAS Pharma Limited (updated)
- Module 1.2 Annex 5.12 - BSE Declaration from Capsugel with updated TSE CEP (updated)
- Module 1.2 Annex 5.22 - QP Declaration from MIAS Pharma Limited (updated)
- Module 1.3.1 Package Leaflet text (updated)
- Module 1.3.2 Package Leaflet mock-up (MIAS)

Module 3

- Module 3.2.S.2.1 Manufacturers (updated)
- Module 3.2.P.3.1 Manufacturers (updated)
- Module 3.2.R.3.2 - BSE Declaration from Capsugel with updated TSE CEPs (updated)

The updated package leaflet text is also provided in 'changes tracked' Word format outside of the eCTD backbone in a separate 'Working Documents' folder.

Please note that the first, third and fourth of the above-mentioned variations was previously submitted to the MHRA in June 2022 as a Type IA Grouping (as sequence 0004). However, this previous submission was determined by the MHRA to be invalid (see attached) due to incorrect categorisation of two of the component variations. As such, this present submission serves to address this previous invalidation, with these variations now appropriately classified. Unfortunately, an oversight occurred in that the MHRA's invalidation notice was initially not seen by the MAH, hence the timing of this present submission. It is noted that the package leaflet mock-up as was included in this previous submission (as dated June 2022) has been and will continue to be used for marketed product going forward, and therefore this version is (re)provided in this present submission to illustrate this currently and prospectively used package leaflet.

Since all five component variations within this submission are of Type IAIN or Type IA it is an appropriate situation, in accordance with Article 7(2)(a) of the variation regulation (Commission Regulation (EC) No 1234/2008), to submit these as a Type IA grouping.

For all five of the component variations, all the conditions and documentary requirements have been met (as displayed in Module 1.2 Variation Application Form).

The MAH can confirm that no other changes have been introduced other than those stated in the Variation Application Form provided and this cover letter.

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This eCTD sequence has been assembled and validated using Lorenz DocuBridge to the standards laid out in the current ICH and EU eCTD specifications. The eCTD sequence has passed the Applicant's internal technical validation (using the Lorenz new eValidator software) and its content has been checked with an up-to-date version of a virus checker (Security Manager AV Defender).

Pharmaxis would be grateful if you could acknowledge receipt of the enclosed documentation. If there are any technical validation issues regarding the submitted eCTD sequence or any queries concerning the administrative or scientific aspects of this application, please do not hesitate to contact me [kristen.morgan@pharmaxis.com.au].

Yours faithfully,

Kristen Morgan
Pharmaxis Europe Limited
Head of Medical & Regulatory Affairs

Tel: +61 (0) 2 9451 7257
Fax: +61 (0)2 9451 3622
E-mail: kristen.morgan@pharmaxis.com.au

Attachment 6 CR- OPS-23-009 KA 7 MAR 2023

REGULATORY NOTIFICATION CHECKLIST FOLLOWING CA APPROVAL

Attachment 6 to change request number (incl. title of the change request): OPS-23-009

Notification of Approval Checklist for **Bronchitol** Approvals – Please update as required for each Notification prior to submission –checking organisation chart as required

Function/ Region	Name	Email	Notification Sent (Yes/No/Comments)	Verified by (Initial/Date)
INTERNAL PHARMAXIS FOR BRONCHITOL AND ARIDOL				
Internal	**Head of Quality** Eddie Vaiciurgis	Eddie.Vaiciurgis@pharmaxis.com.au		
	Operations Manager Dolores Baird	Dolores.Baird@pharmaxis.com.au		
	QA Manager Aaron Dooley	Aaron.Dooley@pharmaxis.com.au		
Internal - Artwork	**Oversight of Artwork** Jonas Makasiar	Jonas.Makasiar@pharmaxis.com.au		
Internal - Medical Team	**John Miller (Medinfo)** Sharon Hammond **(Website)**	John.Miller@pharmaxis.com.au Sharon.Hammond@pharmaxis.com.au		

REGULATORY NOTIFICATION CHECKLIST FOLLOWING CA APPROVAL

	Fiona Frahm **(PV safety)** **PV Manager** Marie-Do Mompass **Jana Baskar** (if required (Chief Medical Officer)	Fiona.Frahm@pharmaxis.co.uk Marie-dominique.mompas@pharmaxis.com jana.baskar@pharmaxis.com.au	N/A UD 9/NOV 23	
EXTERNAL PHARMACOVIGILENCE AND REGULATORY				
Local Responsible Persons	As per MEDFM-118	If there is an update to the Product Information (SmPC) or PIL List those required for notification	N/A	N/A

REGULATORY NOTIFICATION CHECKLIST FOLLOWING CA APPROVAL

Spanish Regulatory Consultants	**Best Pharma** Carla Puigcerver	carla.puigcerver@bestpharma.es vferrando@bestpharma.es Spanish authority needs to be notified with a local process if there is impact on SmPC, PIL or labelling	N/A	N/A
Other Regulatory Consultants or Activities	Such as Local EU Notifications	e.g – Birk for Nordic activities NDA reg for German activities	N/A	N/A
PV-Primevigilance	~~Andreja grgic~~ Rohith Nair	~~andreja.grgic~~@primevigilance.com rohith.nair	N/A	N/A
	General	pharmaxis@primevigilance.com;	N/A	N/A
	Medinfo (as applicable) – Aridol/Osmohale for UK/Ireland and Bronchitol for Austria	MIAssistant@primevigilance.com	N/A	N/A
EU QPPV	Marie-Do Mompass	Marie-dominique.mompas@pharmaxis.com	N/A	N/A
		N/A KD 01 Nov 23		

REGULATORY NOTIFICATION CHECKLIST FOLLOWING CA APPROVAL

BRONCHITOL PARTNER CONTACTS				
Spanish distributor – Chiesi Spain	Mónica VALLS VENTURA	M.VALLS@chiesi.com		
German distributor – Chiesi GmbH	Anja Yang, Anne Pueffel	a.yang@chiesi.com a.pueffel@chiesi.com de-DRA@chiesi.com		
Italian distributor – Chiesi Italy and local regulatory	Atillo Sarzi, Rosa Fazio	A.SarziSartori@chiesi.com r.fazio.consultant@chiesi.com		
Greek distributor – Chiesi Greece	Theodora Nikopoulou	T.NIKOPOULOU@chiesi.com	N/A KD 01 Nov 23	
Norwegian, Swedish and Danish distributor – Chiesi Pharma AB	Eleonor Borg	e.borg@chiesi.com		
Hungarian distributor – Mesasza Kft	Gabor Metzger	metzgergabor@gmail.com	N/A	N/A
Czech Republic distributor – 4 Life Pharma	Romana Rozkova	r.rozkova@4lifepharma.eu	N/A KD 01 Nov 23	
Slovakian distributor – 4 Life Pharma	Denisa Hericova	denisa.hericova@pharmin.sk	N/A	N/A

REGULATORY NOTIFICATION CHECKLIST FOLLOWING CA APPROVAL

AU Distributor (MAH) BTC health	Dianna Mckieman	dmckiernan@btchealth.com.au	Yes	KD 01 Nov 23
Russia, Kazakhstan, Uzbekistan Distributor (MAH) Genilac	Ferda Yıldırım Gürsoy, Kirill Mizerov	f.gursoy@genilac.com; k.mizerov@genilac.com	Yes	KD 01 Nov 23
US Distributor (MAH) Chiesi Inc.	Jessica Anderson (Regulatory Affairs Lead)	jessica.anderson@chiesi.com	N/A	N/A
Swiss Distributor (MAH) EffRx	Christiane Siervert	csievert@effrx.com	N/A	N/A
Brazil (MAH) United Medical/KnightTX	Alessandra Ignácio María Eugenia Cabezas	alessandra.ignacio@knighttx.com eugenia.cabezas@knighttx.com	N/A	N/A
UK distributor – Chiesi Limited	Khayyam Darr, Tony Rigden	K.Darr@chiesi.com; T.Rigden@chiesi.com; regulatory.uk@chiesi.com	N/A	N/A
EU QP for Batch Release - Arvato	QA to notify			

REGULATORY NOTIFICATION CHECKLIST FOLLOWING CA APPROVAL

EU QP for Batch Release - MIAS	QA to notify			
Czech Republic wholesaler – Alliance	QA to notify			
Hungarian wholesaler - Hungaropharma	QA to notify			
UK/EU wholesaler – Chapper	QA to notify			
Russian wholesaler - Medintorg	MAH to Notify		N/A KD 01 Nov 23	
Other Wholesaler/Importer etc	QA to notify			
Emc Database UK & Ireland (and Northern Ireland)	Kristen Morgan	Kristen.Morgan@pharmaxis.com.au	N/A	N/A

REGULATORY NOTIFICATION CHECKLIST FOLLOWING CA APPROVAL

Notification of Approval Checklist for **Aridol** Approvals

Function/ Region	Name	Email	Notification Sent (Yes/No/Comments)	Verified by (Initial/Date)
ARIDOL PARTNERS/DISTRIBUTORS				
Spanish distributor – Aldo-Union	Álvaro Calzada	alvaro@aldo-union.com	N/A	N/A
AU Distributor (MAH) BTC health	Dianna Mckieman	dmckiernan@btchealth.com.au	Yes	KD 01Nov23
Nordic distributor – Birk NPC	Regulatory	regulatory@birk-npc.com	N/A	N/A
	Kjetil Herland	kjetil.herland@birk-npc.com	N/A	N/A
	LINK Medical	NOregulatory@linkmedical.eu	N/A	N/A
South Korea (MAH) – Clinigen Korea, LLC.	Gina Choi Hagyeong Yu	Gina.Choi@clinigen.co.kr Hagyeong.Yu@clinigen.co.kr	N/A	KD 01Nov23
US, Canada – Methapharm	Bernice Tao, Josephine holmes	btao@methapharm.com; JHolmes@methapharm.com	N/A	KD 01Nov23

Attachment D to CR N° OPS-23-009.
Notification of change to Gen.
04 Apr 23

pharmaxis	FM-451-02	Date Effective: 01-Mar-21	Page 1 of 2

EXTERNAL CHANGE CONTROL NOTIFICATION

☑ For customer approval
☐ For information to customer

Change Request No.: OPS-23-009

Section 1) Description of Change

a. Product Details: All Bunchitol products

b. Summary of Change:

The capsugel safety statement on BSE/TSE has been updated as per the attached CR N° OPS-23-009. This impacts the gelatin capsules used for all Bunchitol products.

c. Change Request Actions / Deliverables (Attachment No. CR OPS-23-009)

d. Type of Risk: (please circle) (Quality) / Safety

Assigned Level of Risk: Moderate

Written by: pp. E. Vaicivgs **Date:** 04 Apr 23
Change Request Leader

Sent to Customer by: E. Vaicivgs **Date:** 04 Apr 23

Customer Company Name: Gen

EXTERNAL CHANGE CONTROL NOTIFICATION

☑ For customer approval ☐ For information to customer	Change Request No.: OPS-23-009

Section 2) Customer Approval of Change (if required)

Position Title	Name	Signature	Date

Comments:

Customer Change Control or equivalent number (if applicable): _____

Please cross out any unused lines

Section 3) Customer Acknowledgement of Receipt of Change Control Notification

I acknowledge receipt of the External Change Control Notification

By Customer Quality Representative	**Title:** _____
	Name: _____
	Signature: _____
	Date: _____

Section 4) Pharmaxis

Date Form Received Completed by Customer: _____

Received by: _____

Attach to relevant Change Request Form

Eddie Vaiciurgis

From: Eddie Vaiciurgis
Sent: Tuesday, 4 April 2023 10:56 AM
To: 'Yasin Genç'
Subject: Change Request Notification - Change to Capsule Manufacturer TSE/BSE Statement
Attachments: Gen ECCN for CR No.23-009.pdf

Dear Yasin

Please find attached the external notification change form for CR No.OPS-23-009. This is in regards to the changing of the capsule manufacturer's TSE/BSE statement as described in the attached documentation. Can I get you to review and complete section 2 of the FM-451 and return a scanned copy of this page.

Kind Regards

Eddie Vaiciurgis
Head of Quality
pharmaxis
M: +61 402419291 T: +612 9454 7239 F: +612 9451 3622
A: 20 Rodborough Road, Frenchs Forest NSW 2086
www.pharmaxis.com.au

EXTERNAL CHANGE CONTROL NOTIFICATION

☑ For customer approval
☐ For information to customer

Change Request No.: OPS-23-009.

Section 2) Customer Approval of Change (if required)

Position Title	Name	Signature	Date
Quality Assurance Manager	Jeyney KAYLLOGLU		05.04.2023

Comments: NA

Customer Change Control or equivalent number (if applicable): NA

Please cross out any unused lines

Section 3) Customer Acknowledgement of Receipt of Change Control Notification

I acknowledge receipt of the External Change Control Notification

By Customer Quality Representative

Title: Quality Director

Name: Büreen Uygun

Signature:

Date: 05.04.2023

Section 4) Pharmaxis

Date Form Received Completed by Customer: 11 Apr 23

Received by:

Attach to relevant Change Request Form

pharmaxis	FM-451-02	Date Effective: 01-Mar-21	Page 1 of 2

EXTERNAL CHANGE CONTROL NOTIFICATION

☑ For customer approval
☐ For information to customer

Change Request No.: OPS-23-009

Section 1) Description of Change

a. Product Details: All Branchial products

b. Summary of Change:

The capsuled safety statement on BSE/TSE has been updated as per the attached CR N° OPS-23-009.

c. Change Request Actions / Deliverables (Attachment No. CR OPS-23-009)

d. Type of Risk: (please circle) (Quality) / Safety

Assigned Level of Risk: Moderate

Written by: pp. E. Vaicivgis — **Date:** 04 Apr 23
Change Request Leader

Sent to Customer by: E. Vaicivgis — **Date:** 04 Apr 23

Customer Company Name: Gen

Attachment E to CR N° ORS-23-009
Change N. Micchi to Chiesi US
by email

pharmaxis	FM-451-02	Date Effective: 01-Mar-21	Page 1 of 2

EXTERNAL CHANGE CONTROL NOTIFICATION

☑ For customer approval
☐ For information to customer

Change Request No.: ORS-23-009

Section 1) Description of Change

a. Product Details: Bronchitol US

b. Summary of Change:

The Lonza / Capsugel safety statement on BSE/TSE has been updated as per attached CR N° ORS-23-009.

c. Change Request Actions / Deliverables (Attachment No. ORS-23-009)

d. Type of Risk: (please circle) (Quality) / Safety

Assigned Level of Risk: Moderate

Written by: pp E. Vaicivgis — **Date:** 04 Apr 23
Change Request Leader

Sent to Customer by: E. Vaicivgis — **Date:** 04 Apr 23

Customer Company Name: Chiesi US

EXTERNAL CHANGE CONTROL NOTIFICATION

☑ For customer approval ☐ For information to customer	Change Request No.: CRS-23-009

Section 2) Customer Approval of Change (if required)

Position Title	Name	Signature	Date

Comments:

Customer Change Control or equivalent number (if applicable): _____

Please cross out any unused lines

Section 3) Customer Acknowledgement of Receipt of Change Control Notification

I acknowledge receipt of the External Change Control Notification

By Customer Quality Representative	**Title:** _____
	Name: _____
	Signature: _____
	Date: _____

Section 4) Pharmaxis

Date Form Received Completed by Customer: _____

Received by: _____

Attach to relevant Change Request Form

Eddie Vaiciurgis

From: Eddie Vaiciurgis
Sent: Tuesday, 4 April 2023 9:13 AM
To: 'SCHWARTZMAN Robyn'; CASHMAN Allyson
Subject: CR No.OPS-23-009 for Chiesi Approval
Attachments: CR No,OPS-23-009 External Notification Chiesi US.PDF

Hi Robyn and Allyson

I have attached a new change request for review and approval for a change by Capsugel in their BSE/TSE statement as attached. Can you let us know if this will be handled via submission or through the annual report to FDA? We are getting capsules this week with the updated TSE/BSE statement, so can we get this review done as quick as possible?

Kind Regards

Eddie Vaiciurgis
Head of Quality
pharmaxis
M: +61 402419291 T: +612 9454 7239 F: +612 9451 3622
A: 20 Rodborough Road, Frenchs Forest NSW 2086
www.pharmaxis.com.au

EXTERNAL CHANGE CONTROL NOTIFICATION

☑ For customer approval
☐ For information to customer

Change Request No.: OPS-23-009

Section 2) Customer Approval of Change (if required)

Position Title	Name	Signature	Date
Quality Product Manager	Robyn Schwartzman	[signature]	06APR2023
	NA RNS	06APR2023	

Comments: NA

Customer Change Control or equivalent number (if applicable): PR 204146

Please cross out any unused lines

Section 3) Customer Acknowledgement of Receipt of Change Control Notification

I acknowledge receipt of the External Change Control Notification

By Customer Quality Representative

Title: NA RNS 06APR2023

Name:

Signature:

Date:

Section 4) Pharmaxis

Date Form Received Completed by Customer: 11 Apr 23

Received by: R Vaicunas

Attach to relevant Change Request Form

Attachment 1 to OPS-23-009

Attachment 2 to FM-182-07
Page 1 of 3
Initial RD Date 19Apr23

Description of Change:

Lonza/Capsugel's most recent safety statement on BSE (Bovine Spongiform Encephalopathy)/TSE (Transmissible Spongiform Encephalopathy) has been updated, refer to attachment 2 for reference.

Summary of change:

USA;

Withdrawal of FDA guidance reference:

US FDA - 21 CFR Parts 211, 226, 300, 500, 530, 600, 895, and 1271 related to Use of Material Derived from Cattle in Medicinal Products

Addition of;

United States Department of Agriculture (USDA) – 9 CFR 94.23 Importation of Gelatin Derived from Bovines.

EU;

Currently submitted CEP (2021)	Updated as at Oct 2022	Comments
Rousselot R1-CEP 2000-029 Rev 05		No Change
Rousselot R1-CEP 2010-043 Rev 00		No Change
PB Gelatins R1-CEP 2000-045 Rev 03	PB Gelatins R1-CEP 2000-045 Rev 04	New CEP
Gelita Group R1-CEP 2001-424 Rev 03		No change
Sterling Gelatin R1-CEP 2001-211 Rev 01		No Change
Nitta Gelatin R1-CEP 2000-344 Rev 02	Nitta Gelatin R1-CEP 2000-344 Rev 03	New CEP
Nitta Gelatin R1-CEP 2004-247 Rev 00		Discontinued
Nitta Gelatin R1-CEP 2004-320 Rev 00		Discontinued
Nitta Gelatin R1 CEP 2005-217 Rev 00	Nitta Gelatin R1 CEP 2005-217 Rev 02	New CEP
	Pioneer Jellice R1-CEP 2008-048 Rev 00	New CEP

Risk Assessment:

Risk assessment:

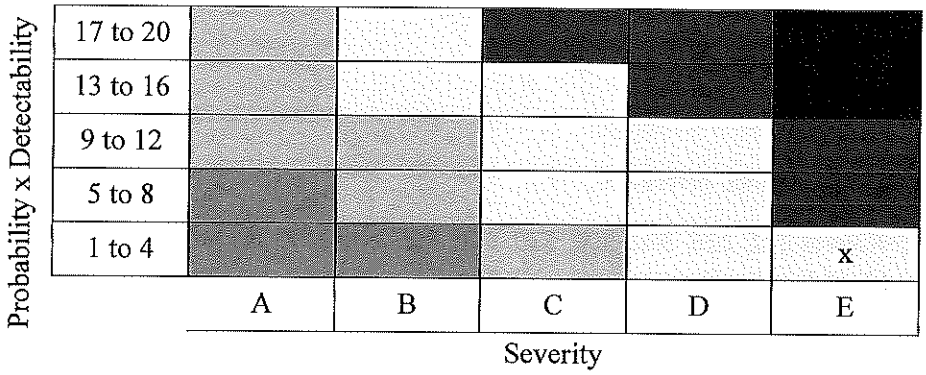
Assigned Severity: E, Catastrophic risk assigned based on potential disease vCJD (human variant of mad cow disease), which is considered fatal.

Assigned Probability: 1 Rare – based on low prevalence of the disease.

Assigned Detectability: 2 High – considered high due to current regulations in place.

Attachment 1 to OPS-23-009

Risk: Moderate



	Indicates assessed as a NEGLIGIBLE RISK
	Indicates assessed as a MINOR RISK
	Indicates assessed as a MODERATE RISK.
	Indicates assessed as a MAJOR RISK
	Indicates assessed as a SEVERE RISK

Enabling a Healthier World

Lonza
Capsules & Health Ingredients

Statement on TSE/BSE safety

Capsugel® empty gelatin based capsule products

Lonza can use blends of several pharmaceutical gelatins of bovine and/or porcine origin, in full compliance with all applicable pharmaceutical and/or food regulatory statutes.

Related to the specific regulations aiming to secure the TSE/BSE safety, Lonza sources bovine gelatin fully complying with the following:

Europe:

- Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3), which is published by the European Commission following Commission Directive 2003/63/EC, (amending Directive 2001/83/EC on the Community code relating to medicinal products for human use), Annex I, Part I, paragraph 3.2.2.4. Control of excipients.
  These Directives require that applicants for Marketing Authorization must demonstrate that medicinal products are manufactured in accordance with the latest version of this Note for Guidance and compliance is demonstrated by the "Certificate of Suitability" issued to the manufacturer of the bovine gelatin by the European Directorate for the Quality of Medicines (EDQM). As such, **from February 1st 2023**, Lonza manufactures capsules under any (or all) of the following Certificates of Suitability:

  - Rousselot R1-CEP 2000-029-Rev 05
  - Rousselot R1-CEP-2010-043-Rev 00
  - Tessenderlo Group R1-CEP 2000-045-Rev 04
  - Gelita Group R1-CEP 2001-424-Rev 03
  - Sterling Gelatin R1-CEP 2001-211-Rev 01
  - Nitta Gelatin R1-CEP 2000-344-Rev 03
  - Nitta Gelatin R1-CEP 2005-217-Rev 02
  - Pioneer Jellice R1-CEP 2008-048-Rev 00

- Regulation (EC) No 853/2004 laying down specific hygiene rules for food of animal origin.
- Regulation (EC) No 999/2001 laying down rules for the prevention, control and eradication of certain transmissible spongiform encephalopathies.

US:

- United States Food and Drug Administration - 21 CFR Part 189 – "Substances Prohibited from Use in Human Food: Prohibited Cattle Materials."
- United States Department of Agriculture (USDA) – 9 CFR 94.23 Importation of Gelatin Derived from Bovines.

10, Rue Timken
FR-68027 Colmar Cedex
T +33 3 89 20 57 09
F +33 3 89 41 48 11

Rijksweg 11
BE-2880 Bornem
T +32 3 890 05 11
F +32 3 889 26 22

535 North Emerald Road
Greenwood, SC 29646 USA
T +1 (888) 783 6361
F +1 (888) 783 6360

Boulevard 18 de Noviembre
1030A
Puebla 72270, México
T +52 (222) 372 1545

Lonza

Capsules & Health Ingredients

Japan:

- Japanese Ministry of Health, Labor Welfare (MHLW) - "Food Sanitation Law", Chapter 2, Article 7 and Article 10 "Specifications and Standards for Food or additives" revised and announced by MHLW Notice No.0327-2 of March 27, 2015.
- Japanese Ministry of Health, Labor and Welfare - Notification No. 210 of the MHLW issued on May 20, 2003 and the latest version by Notification No. 1002-27 about the partial amendment of the criteria eliminating source country restrictions, applicable from November 25th 2014.

The bovine bone starting material is derived from healthy animals that were slaughtered in a slaughterhouse and that passed an ante-mortem and post-mortem inspection by an official veterinarian.

For what concerns specified risk materials (SRMs), next to the removal of skulls and spinal cords, Lonza's bovine bone gelatin suppliers certify vertebrae removal independent from the geographical origin and/or age of the animals.

Lonza continuously monitors all regulatory activities; please let us know if there are further questions or clarification needed.

Revision History:

Last Update	*Update*
September 2015	Actualization of list of applicable CEPs and legislative references
November 2016	Actualization of US Interim Final Rule to Final Rule
July 2017	Introduction R1-CEP-2010-043 and discontinuation R1-CEP 2001-332, R1-CEP 2003-172, R1-CEP 2000-027 and R1-CEP 2002-110 as from October 1st, 2017
June 2019	Update of R1-CEP-2000-045 from Rev03 to Rev04, Update from R1-CEP-2005-217 from Rev00 to Rev01. Discontinuation of R1-CEP-2004-247 and R1-CEP-2004-320
July 2019	Update of R1-CEP-2005-217 from Rev01 to Rev02
October 2019	Update of R1-CEP 2000-344 from Rev02 to Rev03
January 2020	New LONZA template
September 2021	CEPs in attachment replaced by recently signed versions
October 2022	Introduction R1-CEP 2008-048-Rev 00 Update of regulatory references for the United States

For further information, please contact your Account Solutions Representative.

Last update: October, 2022

10, Rue Timken
FR-68027 Colmar Cedex
T +33 3 89 20 57 09
F +33 3 89 41 48 11

Rijksweg 11
BE-2880 Bornem
T +32 3 890 05 11
F +32 3 889 26 22

535 North Emerald Road
Greenwood, SC 29646 USA
T +1 (888) 783 6361
F +1 (888) 783 6360

Boulevard 18 de Noviembre
1030A
Puebla 72270, México
T +52 (222) 372 1545

Attachment A to CR N° OPS-23-009

External CR Notification Clinigen Korea & Aridol Korea

04 Apr 23

pharmaxis	FM-451-02	Date Effective: 01-Mar-21	Page 1 of 2

EXTERNAL CHANGE CONTROL NOTIFICATION

☑ For customer approval
☐ For information to customer

Change Request No.: OPS-23-009

Section 1) Description of Change

a. Product Details: Aridol Korea

b. Summary of Change: The Capsugel/Lonza safety statement on BSE/TSE has been updated as per the attached CR N° OPS-23-009. This impacts gelatin capsules used for Aridol product.

c. Change Request Actions / Deliverables (Attachment No. CR N° OPS-23-009)

d. Type of Risk: (please circle) (Quality) / Safety

Assigned Level of Risk: Moderate

Written by: E. Vaicivuyo **Date:** 04 Apr 23
Change Request Leader

Sent to Customer by: E. Vaicivuyo **Date:** 04 Apr 23

Customer Company Name: Clinigen Korea

EXTERNAL CHANGE CONTROL NOTIFICATION

☑ For customer approval ☐ For information to customer	Change Request No.: OPS-23-004

Section 2) Customer Approval of Change (if required)

Position Title	Name	Signature	Date

Comments:

Customer Change Control or equivalent number (if applicable): _____

Please cross out any unused lines

Section 3) Customer Acknowledgement of Receipt of Change Control Notification

I acknowledge receipt of the External Change Control Notification

By Customer Quality Representative	**Title:** _____
	Name: _____
	Signature: _____
	Date: _____

Section 4) Pharmaxis

Date Form Received Completed by Customer: _____

Received by: _____

Attach to relevant Change Request Form

Eddie Vaiciurgis

From: Eddie Vaiciurgis
Sent: Tuesday, 4 April 2023 10:28 AM
To: Hagyeong Yu
Subject: Change Request document for BSE/TSE Statement Change from Capsule Manufacture
Attachments: Clinigen ECCN CR No.OPS-23-009.pdf

Dear Hagyeong

Please find attached the external change notification form with applicable change request for the change in the BSE/TSE statement you have previously E-mailed was acceptable. Can you review the documents and sign section 2 of FM-451 and return a scanned copy of this page.

Kind Regards

Eddie Vaiciurgis
Head of Quality
pharmaxis
M: +61 402419291 T: +612 9454 7239 F: +612 9451 3622
A: 20 Rodborough Road, Frenchs Forest NSW 2086
www.pharmaxis.com.au

pharmaxis	FM-451-02	Date Effective: 01-Mar-21	Page 1 of 2

EXTERNAL CHANGE CONTROL NOTIFICATION

☑ For customer approval
☐ For information to customer

Change Request No.: OPS-23-009

Section 1) Description of Change

a. Product Details: Aridol Korea

b. Summary of Change: The Capsugel Lonza safety statement on BSE/TSE has been updated as per the attached CR N°. OPS-23-009. This impacts gelatin capsules used for Aridol product.

c. Change Request Actions / Deliverables (Attachment No. CR N° OPS-23-009)

d. Type of Risk: (please circle) (Quality) / Safety

Assigned Level of Risk: Moderate

Written by: E. Vaicivuga Change Request Leader **Date:** 04Apr23

Sent to Customer by: E. Vaicivuga **Date:** 04Apr23

Customer Company Name: Clinigen Korea

EXTERNAL CHANGE CONTROL NOTIFICATION

☑ For customer approval
☐ For information to customer

Change Request No.: CR-23-004

Section 2) Customer Approval of Change (if required)

Position Title	Name	Signature	Date
QA mamager	Hagyeong Yu		4 April 2023

Comments: NA

Customer Change Control or equivalent number (if applicable): NA

Please cross out any unused lines

Section 3) Customer Acknowledgement of Receipt of Change Control Notification

I acknowledge receipt of the External Change Control Notification

By Customer Quality Representative

Title: _____

Name: No reply 4Apr23

Signature: _____

Date: _____

Section 4) Pharmaxis

Date Form Received Completed by Customer: 04 Apr 23

Received by: E. Vaicius

Attach to relevant Change Request Form

Attachment B to CR N° CRS-23-009

Extend CR Notification to BTC Health for Aridol Australia & Branchitol Australia.

04Apr23

pharmaxis	FM-451-02	Date Effective: 01-Mar-21	Page 1 of 2

EXTERNAL CHANGE CONTROL NOTIFICATION

☐ For customer approval
☑ For information to customer

Change Request No.: CR N° CRS-23-009

Section 1) Description of Change

a. Product Details: Branchitol & Aridol Products for Australia

b. Summary of Change: The Capsugel/Lonza safety statement on BSE/TSE has been updated as per attached CR N° CRS-23-009. This impacts gelatin capsules to be used for all Aridol & Branchitol products.

c. Change Request Actions / Deliverables (Attachment No. CRCRS-23-009)

d. Type of Risk: (please circle) (Quality) / Safety

Assigned Level of Risk: Moderate

Written by: pp E. Vaicunas **Date:** 04Apr23
Change Request Leader

Sent to Customer by: E. Vaicunas **Date:** 04Apr23

Customer Company Name: BTC

EXTERNAL CHANGE CONTROL NOTIFICATION

☐ For customer approval ☑ For information to customer	Change Request No.: CR N° UPS-23-009

Section 2) Customer Approval of Change (if required)

Position Title	Name	Signature	Date
	Not Required by QA Apr-23		

Comments:

Customer Change Control or equivalent number (if applicable): _____

Please cross out any unused lines

Section 3) Customer Acknowledgement of Receipt of Change Control Notification

I acknowledge receipt of the External Change Control Notification

By Customer Quality Representative	**Title:** _____
	Name: _____
	Signature: _____
	Date: _____

Section 4) Pharmaxis

Date Form Received Completed by Customer: _____

Received by: _____

Attach to relevant Change Request Form

Eddie Vaiciurgis

From: Eddie Vaiciurgis
Sent: Tuesday, 4 April 2023 10:34 AM
To: 'Dianna McKiernan'
Subject: RE: Change Request Notification - Change to Capsule Manufacturer TSE/BSE Statement
Attachments: BTC ECCN for CR No.OPS-23-009.pdf

Apologies

This time with the attached document.

Eddie

From: Eddie Vaiciurgis
Sent: Tuesday, 4 April 2023 10:33 AM
To: 'Dianna McKiernan' <dmckiernan@btchealth.com.au>
Subject: Change Request Notification - Change to Capsule Manufacturer TSE/BSE Statement

Dear Dianna

Please find attached the external notification change form for CR No.OPS-23-009. This is in regards to the changing of the capsule manufacturer's TSE/BSE statement as described in the attached documentation. Can I get you to complete section 3 of the FM-451 and return a scanned copy of this page.

Kind Regards

Eddie Vaiciurgis
Head of Quality
pharmaxis
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A: 20 Rodborough Road, Frenchs Forest NSW 2086
www.pharmaxis.com.au

EXTERNAL CHANGE CONTROL NOTIFICATION

☐ For customer approval ☑ For information to customer	Change Request No.: CR N° QPS-23-009

Section 2) Customer Approval of Change (if required)

Position Title	Name	Signature	Date
	Not Required	04 Apr 23	

Comments:

Customer Change Control or equivalent number (if applicable): _____

Please cross out any unused lines

Section 3) Customer Acknowledgement of Receipt of Change Control Notification

I acknowledge receipt of the External Change Control Notification

By Customer Quality Representative	**Title:** Senior Quality and Regulatory Affairs Manager
	Name: Dianna McKiernan
	Signature:
	Date: 04 April 2023

Section 4) Pharmaxis

Date Form Received Completed by Customer: 05-Apr-23

Received by: [signature]

Attach to relevant Change Request Form

Attachment C to CR N° OPS-23-009

Change Notification to EQPR, regarding Benchtel Switzerland.

04Apr23

pharmaxis	FM-451-02	Date Effective: 01-Mar-21	Page 1 of 2

EXTERNAL CHANGE CONTROL NOTIFICATION

☑ For customer approval

☐ For information to customer

Change Request No.: OPS-23-009

Section 1) Description of Change

a. Product Details: Benchtel Switzerland

b. Summary of Change:

The Capsugel safety statement on BSE/TSE has been updated as per the attached CR N° OPS-23-009. This will impact gelatin capsules to be used for Benchtel Switzerland product.

c. Change Request Actions / Deliverables (Attachment No. CR OPS-23-009)

d. Type of Risk: (please circle) (Quality) / Safety

Assigned Level of Risk: Moderate

Written by: E. Vaicunga (Change Request Leader) **Date:** 04Apr23

Sent to Customer by: E. Vaicunga **Date:** 04 Apr 23

Customer Company Name: EQPR

EXTERNAL CHANGE CONTROL NOTIFICATION

☑ For customer approval

☐ For information to customer

Change Request No.: OPS-23-009

Section 2) Customer Approval of Change (if required)

Position Title	Name	Signature	Date

Comments:

Customer Change Control or equivalent number (if applicable): _____

Please cross out any unused lines

Section 3) Customer Acknowledgement of Receipt of Change Control Notification

I acknowledge receipt of the External Change Control Notification

By Customer Quality Representative	**Title:** _____
	Name: _____
	Signature: _____
	Date: _____

Section 4) Pharmaxis

Date Form Received Completed by Customer: _____

Received by: _____

Attach to relevant Change Request Form

Eddie Vaiciurgis

From: Eddie Vaiciurgis
Sent: Tuesday, 4 April 2023 10:42 AM
To: Nathalie Véron
Subject: Change Request Notification - Change to Capsule Manufacturer TSE/BSE Statement
Attachments: EffRx ECCN For CR No.OPS-23-009.pdf

Dear Nathalie

Please find attached the external notification change form for CR No.OPS-23-009. This is in regards to the changing of the capsule manufacturer's TSE/BSE statement as described in the attached documentation. Can I get you to review and complete section 2 of the FM-451 and return a scanned copy of this page.

Kind Regards

Eddie Vaiciurgis
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Eddie Vaiciurgis

From: Nathalie Véron <nveron@effrx.com>
Sent: Thursday, 6 April 2023 10:20 PM
To: Eddie Vaiciurgis
Subject: RE: Change Request Notification - Change to Capsule Manufacturer TSE/BSE Statement
Attachments: EffRx ECCN For CR No.OPS-23-009-approval QP EffRx.pdf

Dear Eddie,

thanks a lot for sharing the change control for OPS-23-009, please find attached the signed approval page attached.
Best Regards
Nathalie

Dr. Nathalie Véron
Director Technical Operations & Qualified Person
Direct +41 44 503 78 61
Mobile +41 76 749 1667
nveron@effrx.com

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Member of
WODA World Orphan Drug Alliance

From: Eddie Vaiciurgis <Eddie.Vaiciurgis@pharmaxis.com.au>
Sent: Tuesday, 4 April 2023 02:42
To: Nathalie Véron <nveron@effrx.com>
Subject: Change Request Notification - Change to Capsule Manufacturer TSE/BSE Statement

Dear Nathalie

Please find attached the external notification change form for CR No.OPS-23-009. This is in regards to the changing of the capsule manufacturer's TSE/BSE statement as described in the attached documentation. Can I get you to review and complete section 2 of the FM-451 and return a scanned copy of this page.

Kind Regards

Eddie Vaiciurgis
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EXTERNAL CHANGE CONTROL NOTIFICATION

☑ For customer approval ☐ For information to customer	Change Request No.: 023-23-001.

Section 2) Customer Approval of Change (if required)

Position Title	Name	Signature	Date
Qualified Person	Nathalie VERON	N. Veron	06.04.2023

Comments: N/A

Customer Change Control or equivalent number (if applicable): CC 76

Please cross out any unused lines

Section 3) Customer Acknowledgement of Receipt of Change Control Notification

I acknowledge receipt of the External Change Control Notification

By Customer Quality Representative	
	Title: QP
	Name: N. VERON
	Signature: N. Veron
	Date: 06.04.2023

Section 4) Pharmaxis

Date Form Received Completed by Customer: 11 Apr 23

Received by:

Attach to relevant Change Request Form

pharmaxis	FM-451-02	Date Effective: 01-Mar-21	Page 1 of 2

EXTERNAL CHANGE CONTROL NOTIFICATION

☑ For customer approval
☐ For information to customer

Change Request No.: OPS-23-009

Section 1) Description of Change

a. **Product Details:** Benchtel Switzerland

b. **Summary of Change:**

The capsugel safety statement on BSE/TSE has been updated as per the attached CR N° OPS-23-009. This will impact gelatin capsules to be used for Benchtel Switzerland product.

c. **Change Request Actions / Deliverables** (Attachment No. CR OPS-23-009)

d. **Type of Risk:** (please circle) (Quality) / Safety

Assigned Level of Risk: Moderate

Written by: pp E. Vaicunga (Change Request Leader) **Date:** 04 Apr 23

Sent to Customer by: E. Vaicunga **Date:** 04 Apr 23

Customer Company Name: EPR

Authorisation signature and date: 02 Feb 21 | Reference: SOP-022

Attachment F to CR N° OPS-23-009
Extent CR Notification for MIAS Pharma
04 Apr 23

pharmaxis	FM-451-02	Date Effective: 01-Mar-21	Page 1 of 2

EXTERNAL CHANGE CONTROL NOTIFICATION

☐ For customer approval
☑ For information to customer

Change Request No.: OPS-23-009

Section 1) Description of Change

a. Product Details: Benchtop & Andul products

b. Summary of Change:

The Capsugel safety statement on BSE/TSE has been updated as per attached

CR N° OPS-23-009

c. Change Request Actions / Deliverables (Attachment No. CR OPS-23-009)

d. Type of Risk: (please circle) (Quality) / Safety

Assigned Level of Risk: Moderate

Written by: pp E. Vaicivgs **Date:** 04 Apr 23
Change Request Leader

Sent to Customer by: E. Vaicivgs **Date:** 04 Apr 23

Customer Company Name: MIAS Pharma

EXTERNAL CHANGE CONTROL NOTIFICATION

☐ For customer approval
☑ For information to customer

Change Request No.: CRS-23-009

Section 2) Customer Approval of Change (if required)

Position Title	Name	Signature	Date

Comments: Not Required 30/Apr/23

Customer Change Control or equivalent number (if applicable): _____

Please cross out any unused lines

Section 3) Customer Acknowledgement of Receipt of Change Control Notification

I acknowledge receipt of the External Change Control Notification

By Customer Quality Representative	**Title:** _____
	Name: _____
	Signature: _____
	Date: _____

Section 4) Pharmaxis

Date Form Received Completed by Customer: _____

Received by: _____

Attach to relevant Change Request Form

Eddie Vaiciurgis

From: Eddie Vaiciurgis
Sent: Tuesday, 4 April 2023 11:17 AM
To: 'Christine Lowry'
Subject: Change Request Notification - Change to Capsule Manufacturer TSE/BSE Statement
Attachments: MIAS ECCN for CR No.OPS-23-009.pdf

Dear Christine

Please find attached the external notification change form for CR No.OPS-23-009. This is in regards to the changing of the capsule manufacturer's TSE/BSE statement as described in the attached documentation. Can I get you to complete section 3 of the FM-451 and return a scanned copy of this page.

Kind Regards

Eddie Vaiciurgis
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EXTERNAL CHANGE CONTROL NOTIFICATION

☐ For customer approval
☑ For information to customer

Change Request No.: 05-23-009

Section 2) Customer Approval of Change (if required)

Position Title	Name	Signature	Date

Comments: Not Required 04Apr23

Customer Change Control or equivalent number (if applicable): _____

Please cross out any unused lines

Section 3) Customer Acknowledgement of Receipt of Change Control Notification

I acknowledge receipt of the External Change Control Notification

By Customer Quality Representative

Title: QP

Name: CHRISTINE LOWRY

Signature: [signature]

Date: 04 April 2023

Section 4) Pharmaxis

Date Form Received Completed by Customer: 05-Apr-23

Received by: [signature]

Attach to relevant Change Request Form

Attachment F to CR N° OPS-23-009

Extend CR notification to Methapharm for Aridol US & Aridol Canada.

04 Apr 23

pharmaxis	FM-451-02	Date Effective: 01-Mar-21	Page 1 of 2

EXTERNAL CHANGE CONTROL NOTIFICATION

☐ For customer approval

☑ For information to customer

Change Request No.: OPS-23-009

Section 1) Description of Change

a. Product Details: Aridol US & Canada

b. Summary of Change:

The capsule manufacturer has updated their BSE/TSE safety statement as per the attached CR N° OPS-23-009. This impacts gelatin capsules used for all Aridol products manufactured by Pharmaxis.

c. Change Request Actions / Deliverables (Attachment No. CR OPS-23-009)

d. Type of Risk: (please circle) (Quality) / Safety

Assigned Level of Risk: Moderate

Written by: pp E. Vaicivgys **Date:** 04 Apr 23
Change Request Leader

Sent to Customer by: pp E. Vaicivgys **Date:** 04 Apr 23

Customer Company Name: Methapharm

EXTERNAL CHANGE CONTROL NOTIFICATION

☐ For customer approval

☑ For information to customer

Change Request No.: CR-23-009

Section 2) Customer Approval of Change (if required)

Position Title	Name	Signature	Date
	Not Required	D 03 Apr 23	

Comments:

Customer Change Control or equivalent number (if applicable): _____

Please cross out any unused lines

Section 3) Customer Acknowledgement of Receipt of Change Control Notification

I acknowledge receipt of the External Change Control Notification

By Customer Quality Representative	Title: _____
	Name: _____
	Signature: _____
	Date: _____

REFER TO ATTACHED RETURNED PAGE 2 D 11/5/23

Section 4) Pharmaxis

Date Form Received Completed by Customer: _____

Received by: _____

Attach to relevant Change Request Form

Eddie Vaiciurgis

From: Eddie Vaiciurgis
Sent: Tuesday, 4 April 2023 11:22 AM
To: Kristy Moffatt
Subject: Change Request Notification - Change to Capsule Manufacturer TSE/BSE Statement
Attachments: Methapharm ECCN CR No.23-009.pdf

Dear Kristy

Please find attached the external notification change form for CR No.OPS-23-009. This is in regards to the changing of the capsule manufacturer's TSE/BSE statement as described in the attached documentation. Can I get you to complete section 3 of the FM-451 and return a scanned copy of this page.

Kind Regards

Eddie Vaiciurgis
Head of Quality
pharmaxis
M: +61 402419291 T: +612 9454 7239 F: +612 9451 3622
A: 20 Rodborough Road, Frenchs Forest NSW 2086
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EXTERNAL CHANGE CONTROL NOTIFICATION

☐ For customer approval
☑ For information to customer

Change Request No.: CR-23-004

Section 2) Customer Approval of Change (if required)

Position Title	Name	Signature	Date
	Not Required	03 Apr 23	

Comments:

Customer Change Control or equivalent number (if applicable): _____

Please cross out any unused lines

Section 3) Customer Acknowledgement of Receipt of Change Control Notification

I acknowledge receipt of the External Change Control Notification

By Customer Quality Representative

Title: Manager, Quality Assurance
Name: kristy moffatt
Signature: KMoffatt
Date: AUGUST 11. 2023

Section 4) Pharmaxis

Date Form Received Completed by Customer: 14 Aug 23

Received by: _____

Attach to relevant Change Request Form

Attachment # 8 to OPS-23-009 KD 05 Jul 23

Khrystyna Dunn

From: Khrystyna Dunn
Sent: Monday, March 6, 2023 11:08 AM
To: 'Bengül Bıyık'; Ferda Yıldırım Gürsoy; 'Liubov Kalmykova'; 'e.yambulatova@yandex.ru'
Cc: Kristen Morgan; Nadir Ulu
Subject: Bronchitol - CEP update OPS-23-009
Attachments: BSE safety_Rx_HN_HGC_CEPs_valid from Feb2023 attachment 2.pdf

Dear colleagues,

Please be aware that the Lonza/Capsugel's most recent safety statement on BSE (Bovine Spongiform Encephalopathy)/TSE (Transmissible Spongiform Encephalopathy) has been updated and effective from Feb2023 (please find in the attachment).

Please find summary of changes below

Currently submitted CEP V. 2019	Updated as at CEP V. 2022	Comments
Rousselot R1-CEP 2000-029 Rev 05		No Change
Rousselot R1-CEP 2010-043 Rev 00		No Change
Tessenderlo Group R1-CEP 2000-045 Rev 04		No Change
Gelita Group R1-CEP 2001-424 Rev 03		No change
Sterling Gelatin R1-CEP 2001-211 Rev 01		No Change
Nitta Gelatin R1-CEP 2000-344 Rev 03		No Change
Nitta Gelatin R1 CEP 2005-217 Rev 02		No Change
	Pioneer Jellice R1-CEP 2008-048 Rev 00	New CEP

Please let me know if this change require a variation submission in Russia/ Kazakhstan/ Uzbekistan/ Azerbaijan.

Best regards,

Khrystyna Dunn
Regulatory Affairs Associate

pharmaxis

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A: 20 Rodborough Road, Frenchs Forest NSW 2086
www.pharmaxis.com.au

Attachment #8 to OPS-23-009 KD 05 Jul 23

Khrystyna Dunn

From: Khrystyna Dunn
Sent: Monday, March 6, 2023 12:00 PM
To: 'dmckiernan@btchealth.com.au'
Cc: Kristen Morgan; Erin Lin Qiao
Subject: Aridol/Bronchitol - CEP update - OPS-23-009
Attachments: BSE safety_Rx_HN_HGC_CEPs_valid from Feb2023.pdf

Dear Dianna,

Please be aware that the Lonza/Capsugel's most recent safety statement on BSE/TSE has been updated and effective from Feb2023 (please find in the attachment).

Please find summary of changes below

Currently submitted CEP V. 2019	Updated as at CEP V. 2022	Comments
Rousselot R1-CEP 2000-029 Rev 05		No Change
Rousselot R1-CEP 2010-043 Rev 00		No Change
Tessenderlo Group R1-CEP 2000-045 Rev 04		No Change
Gelita Group R1-CEP 2001-424 Rev 03		No change
Sterling Gelatin R1-CEP 2001-211 Rev 01		No Change
Nitta Gelatin R1-CEP 2000-344 Rev 03		No Change
Nitta Gelatin R1 CEP 2005-217 Rev 02		No Change
	Pioneer Jellice R1-CEP 2008-048 Rev 00	New CEP

Please let me know if this change require a variation submission in the TGA.

Best regards,

Khrystyna Dunn
Regulatory Affairs Associate

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A: 20 Rodborough Road, Frenchs Forest NSW 2086
www.pharmaxis.com.au

Attachment # 8 to OPS-23-009 KD 05 Jul 23

Khrystyna Dunn

From: Khrystyna Dunn
Sent: Monday, March 6, 2023 1:24 PM
To: 'Gina.Choi@clinigen.co.kr'; 'Hagyeong.Yu@clinigen.co.kr'
Cc: Kristen Morgan; Erin Lin Qiao
Subject: Aridol - CEP update - OPS-23-009
Attachments: BSE safety_Rx_HN_HGC_CEPs_valid from Feb2023.pdf

Dear Gina,

Please be aware that the Lonza/Capsugel's most recent safety statement on BSE/TSE has been updated and effective from Feb2023 (please find in the attachment).

Please find summary of changes below

Currently submitted CEP (2021)	Updated as at Oct 2022	Comments
Rousselot R1-CEP 2000-029 Rev 05		No Change
Rousselot R1-CEP 2010-043 Rev 00		No Change
PB Gelatins R1-CEP 2000-045 Rev 03	PB Gelatins R1-CEP 2000-045 Rev 04	New CEP
Gelita Group R1-CEP 2001-424 Rev 03		No change
Sterling Gelatin R1-CEP 2001-211 Rev 01		No Change
Nitta Gelatin R1-CEP 2000-344 Rev 02	Nitta Gelatin R1-CEP 2000-344 Rev 03	New CEP
Nitta Gelatin R1-CEP 2004-247 Rev 00		Discontinued
Nitta Gelatin R1-CEP 2004-320 Rev 00		Discontinued
Nitta Gelatin R1 CEP 2005-217 Rev 00	Nitta Gelatin R1 CEP 2005-217 Rev 02	New CEP
	Pioneer Jellice R1-CEP 2008-048 Rev 00	New CEP

Please let me know if this change require a variation submission and what documents required.

Best regards,

Khrystyna Dunn
Regulatory Affairs Associate

pharmaxis

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A: 20 Rodborough Road, Frenchs Forest NSW 2086
www.pharmaxis.com.au

Attachment # 8 to OPS-23-009 KD 05 Jul 23

Khrystyna Dunn

From: Khrystyna Dunn
Sent: Monday, March 6, 2023 1:41 PM
To: 'csievert@effrx.com'
Cc: Kristen Morgan
Subject: Bronchitol - CEP update - OPS-23-009
Attachments: BSE safety_Rx_HN_HGC_CEPs_valid from Feb2023.pdf

Dear Christiane,

Please be aware that the Lonza/Capsugel's most recent safety statement on BSE/TSE has been updated and effective from Feb2023 (please find in the attachment).

Please find summary of changes below

Currently submitted CEP V. 2019	Updated as at CEP V. 2022	Comments
Rousselot R1-CEP 2000-029 Rev 05		No Change
Rousselot R1-CEP 2010-043 Rev 00		No Change
Tessenderlo Group R1-CEP 2000-045 Rev 04		No Change
Gelita Group R1-CEP 2001-424 Rev 03		No change
Sterling Gelatin R1-CEP 2001-211 Rev 01		No Change
Nitta Gelatin R1-CEP 2000-344 Rev 03		No Change
Nitta Gelatin R1 CEP 2005-217 Rev 02		No Change
	Pioneer Jellice R1-CEP 2008-048 Rev 00	New CEP

Please let me know if this change require a variation submission.

Best regards,

Khrystyna Dunn
Regulatory Affairs Associate

pharmaxis

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www.pharmaxis.com.au

Attachment # 8 to OPS-23-009 KD 05 Jul 23

Khrystyna Dunn

From: Khrystyna Dunn
Sent: Monday, March 6, 2023 3:51 PM
To: 'Hagyeong Yu'
Cc: Kristen Morgan; Gina Choi; Erin Lin Qiao
Subject: RE: Aridol - CEP update - OPS-23-009

Dear Hagyeong,

Thank you for your prompt response.

Best regards,

Khrystyna Dunn
Regulatory Affairs Associate

pharmaxis

T: +61421 9338 28 F: +612 9451 3622
A: 20 Rodborough Road, Frenchs Forest NSW 2086
www.pharmaxis.com.au

From: Hagyeong Yu <Hagyeong.Yu@clinigen.co.kr>
Sent: Monday, March 6, 2023 3:03 PM
To: Khrystyna Dunn <Khrystyna.dunn@pharmaxis.com.au>
Cc: Kristen Morgan <Kristen.Morgan@pharmaxis.com.au>; Gina Choi <Gina.Choi@clinigen.co.kr>; Erin Lin Qiao <ErinLin.Qiao@pharmaxis.com.au>
Subject: RE: Aridol - CEP update - OPS-23-009

Dear Khrystyna,

Thank you for your email.
I can confirm this change doesn't require any variation submission.

Thank you.

Best regards,
Hagyeong

Hagyeong Yu
Quality Assurance Manager
Clinigen Korea, LLC.
#606, 6F, Daeryungtechnotown 19th, 70, Gasan digital 2-ro, Geumcheon-gu, Seoul, Korea 08589
Tel.: +82 2 2088 1152

From: Gina Choi <Gina.Choi@clinigen.co.kr>
Sent: Monday, March 6, 2023 11:59 AM
To: Khrystyna Dunn <Khrystyna.dunn@pharmaxis.com.au>; Hagyeong Yu <Hagyeong.Yu@clinigen.co.kr>

Attachment # 8 to OPS-23-009 KD 05 Jul 23

Cc: Kristen Morgan <Kristen.Morgan@pharmaxis.com.au>; Erin Lin Qiao <ErinLin.Qiao@pharmaxis.com.au>
Subject: RE: Aridol - CEP update - OPS-23-009

Dear Khrystyna,

Please direct all RA issues to Hagyeong ☺

@Hagyeong Yu Please respond to the below.

Best regards,
Gina

From: Khrystyna Dunn <Khrystyna.dunn@pharmaxis.com.au>
Sent: Monday, March 6, 2023 11:24 AM
To: Gina Choi <Gina.Choi@clinigen.co.kr>; Hagyeong Yu <Hagyeong.Yu@clinigen.co.kr>
Cc: Kristen Morgan <Kristen.Morgan@pharmaxis.com.au>; Erin Lin Qiao <ErinLin.Qiao@pharmaxis.com.au>
Subject: Aridol - CEP update - OPS-23-009

Dear Gina,

Please be aware that the Lonza/Capsugel's most recent safety statement on BSE/TSE has been updated and effective from Feb2023 (please find in the attachment).

Please find summary of changes below

Currently submitted CEP (2021)	Updated as at Oct 2022	Comments
Rousselot R1-CEP 2000-029 Rev 05		No Change
Rousselot R1-CEP 2010-043 Rev 00		No Change
PB Gelatins R1-CEP 2000-045 Rev 03	PB Gelatins R1-CEP 2000-045 Rev 04	New CEP
Gelita Group R1-CEP 2001-424 Rev 03		No change
Sterling Gelatin R1-CEP 2001-211 Rev 01		No Change
Nitta Gelatin R1-CEP 2000-344 Rev 02	Nitta Gelatin R1-CEP 2000-344 Rev 03	New CEP
Nitta Gelatin R1-CEP 2004-247 Rev 00		Discontinued
Nitta Gelatin R1-CEP 2004-320 Rev 00		Discontinued
Nitta Gelatin R1 CEP 2005-217 Rev 00	Nitta Gelatin R1 CEP 2005-217 Rev 02	New CEP
	Pioneer Jellice R1-CEP 2008-048 Rev 00	New CEP

Please let me know if this change require a variation submission and what documents required.

Best regards,

Khrystyna Dunn
Regulatory Affairs Associate

pharmaxis

T: +61421 9338 28 F: +612 9451 3622
A: 20 Rodborough Road, Frenchs Forest NSW 2086
www.pharmaxis.com.au

Attachment #8 to OPS-23-009 KD 05 Jul 23

Khrystyna Dunn

From: Khrystyna Dunn
Sent: Tuesday, March 7, 2023 2:47 PM
To: 'alessandra.ignacio@knighttx.com'; 'eugenia.cabezas@knighttx.com'
Cc: Kristen Morgan
Subject: Bronchitol - CEP update - OPS-23-009
Attachments: BSE safety_Rx_HN_HGC_CEPs_valid from Feb2023.pdf

Dear Alessandra/ Maria,

Please be aware that the Lonza/Capsugel's most recent safety statement on BSE/TSE has been updated and effective from Feb2023 (please find in the attachment).

Please find summary of changes below

Currently submitted CEP (2011)	Updated as at Oct 2022	Comments
Rousselot SAS R1-CEP 2000-027 Rev		Discontinued
Rousselot SAS R1-CEP 2001-332 Rev		Discontinued
PB Gelatins R1-CEP 2002-110 Rev		Discontinued
PB Leiner R1-CEP 2004-022 Rev		Discontinued
Gelita Group R1-CEP 2003-172 Rev		Discontinued
Sterling Gelatin R1-CEP 2001-211 Rev 01		No Change
Nitta Gelatin R1-CEP 2000-344 Rev 02	Nitta Gelatin R1-CEP 2000-344 Rev 03	New CEP
Nitta Gelatin R1-CEP 2004-247 Rev 00		Discontinued
Nitta Gelatin R1-CEP 2004-320 Rev 00		Discontinued
Nitta Gelatin R1 CEP 2005-217 Rev 00	Nitta Gelatin R1 CEP 2005-217 Rev 02	New CEP
	PB Gelatins R1-CEP 2000-045 Rev 04	New CEP
	Rousselot R1-CEP 2000-029 Rev 05	New CEP
	Rousselot R1-CEP 2010-043 Rev 00	New CEP
	Gelita Group R1-CEP 2001-424 Rev 03	New CEP
	Pioneer Jellice R1-CEP 2008-048 Rev 00	New CEP

Best regards,

Khrystyna Dunn
Regulatory Affairs Associate

pharmaxis

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A: 20 Rodborough Road, Frenchs Forest NSW 2086
www.pharmaxis.com.au

Attachment # 8 to OPS-23-009 KD 05 Jul 23

Khrystyna Dunn

From: Khrystyna Dunn
Sent: Tuesday, March 7, 2023 2:53 PM
To: 'jessica.anderson@chiesi.com'
Cc: Kristen Morgan
Subject: Bronchitol - CEP update - OPS-23-009
Attachments: BSE safety_Rx_HN_HGC_CEPs_valid from Feb2023.pdf

Dear Jessica,

Please be aware that the Lonza/Capsugel's most recent safety statement on BSE/TSE has been updated and effective from Feb2023 (please find in the attachment).
Please let me know if this change require a submission.

Best regards,

Khrystyna Dunn
Regulatory Affairs Associate

pharmaxis

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A: 20 Rodborough Road, Frenchs Forest NSW 2086
www.pharmaxis.com.au

Attachment # 8 to OPS-23-009 KD 05 Jul 23

Khrystyna Dunn

From: Khrystyna Dunn
Sent: Saturday, March 11, 2023 6:01 PM
To: 'María Eugenia Cabezas'
Cc: Kristen Morgan; Alessandra Ignácio
Subject: RE: Bronchitol - CEP update - OPS-23-009

Dear Eugenia,

Apologies for the mistake in the name of the product. Portebro is correct. Bronchitol is our internal name.
CEP update sent for information purpose only. No actions required.

Best regards,

Khrystyna Dunn
Regulatory Affairs Associate

pharmaxis

T: +61421 9338 28 F: +612 9451 3622
A: 20 Rodborough Road, Frenchs Forest NSW 2086
www.pharmaxis.com.au

From: María Eugenia Cabezas <eugenia.cabezas@knighttx.com>
Sent: Tuesday, March 7, 2023 11:36 PM
To: Khrystyna Dunn <Khrystyna.dunn@pharmaxis.com.au>
Cc: Kristen Morgan <Kristen.Morgan@pharmaxis.com.au>; Alessandra Ignácio <alessandra.ignacio@knighttx.com>
Subject: RE: Bronchitol - CEP update - OPS-23-009

Dear Khrystyna, hope you are doing well.

Apologies but we are a little lost here. What is the relation with Portebro product?

We will appreciate your comments to better understand this.

Best regards,

M. Eugenia

De: Khrystyna Dunn <Khrystyna.dunn@pharmaxis.com.au>
Enviado el: martes, 7 de marzo de 2023 0:47
Para: Alessandra Ignácio <alessandra.ignacio@knighttx.com>; María Eugenia Cabezas <eugenia.cabezas@knighttx.com>
CC: Kristen Morgan <Kristen.Morgan@pharmaxis.com.au>
Asunto: Bronchitol - CEP update - OPS-23-009

Dear Alessandra/ Maria,

Attachment # 8 to OPS-23-009 KD 05 Jul 23

Please be aware that the Lonza/Capsugel's most recent safety statement on BSE/TSE has been updated and effective from Feb2023 (please find in the attachment).

Please find summary of changes below

Currently submitted CEP (2011)	Updated as at Oct 2022	Comments
Rousselot SAS R1-CEP 2000-027 Rev		Discontinued
Rousselot SAS R1-CEP 2001-332 Rev		Discontinued
PB Gelatins R1-CEP 2002-110 Rev		Discontinued
PB Leiner R1-CEP 2004-022 Rev		Discontinued
Gelita Group R1-CEP 2003-172 Rev		Discontinued
Sterling Gelatin R1-CEP 2001-211 Rev 01		No Change
Nitta Gelatin R1-CEP 2000-344 Rev 02	Nitta Gelatin R1-CEP 2000-344 Rev 03	New CEP
Nitta Gelatin R1-CEP 2004-247 Rev 00		Discontinued
Nitta Gelatin R1-CEP 2004-320 Rev 00		Discontinued
Nitta Gelatin R1 CEP 2005-217 Rev 00	Nitta Gelatin R1 CEP 2005-217 Rev 02	New CEP
	PB Gelatins R1-CEP 2000-045 Rev 04	New CEP
	Rousselot R1-CEP 2000-029 Rev 05	New CEP
	Rousselot R1-CEP 2010-043 Rev 00	New CEP
	Gelita Group R1-CEP 2001-424 Rev 03	New CEP
	Pioneer Jellice R1-CEP 2008-048 Rev 00	New CEP

Best regards,

Khrystyna Dunn
Regulatory Affairs Associate

pharmaxis

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A: 20 Rodborough Road, Frenchs Forest NSW 2086
www.pharmaxis.com.au

Attachment # 8 to OPS-23-009 KD 05 Jul 23

Khrystyna Dunn

From: Khrystyna Dunn
Sent: Monday, March 13, 2023 12:27 PM
To: 'Bengül Bıyık'
Cc: Kristen Morgan; Nadir Ulu; Ferda Yıldırım Gürsoy; 'e.yambulatova@yandex.ru'
Subject: RE: Bronchitol - CEP update OPS-23-009

Dear Bengul,

Thank you for the update.

Best regards,

Khrystyna Dunn
Regulatory Affairs Associate

pharmaxis

T: +61421 9338 28 F: +612 9451 3622
A: 20 Rodborough Road, Frenchs Forest NSW 2086
www.pharmaxis.com.au

From: Bengül Bıyık <b.biyik@genilac.com>
Sent: Friday, March 10, 2023 5:41 PM
To: Khrystyna Dunn <Khrystyna.dunn@pharmaxis.com.au>
Cc: Kristen Morgan <Kristen.Morgan@pharmaxis.com.au>; Nadir Ulu <n.ulu@genilac.com>; Ferda Yıldırım Gürsoy <f.gursoy@genilac.com>; 'e.yambulatova@yandex.ru' <e.yambulatova@yandex.ru>
Subject: RE: Bronchitol - CEP update OPS-23-009

Dear Khrystyna,

Regarding the variation below, in Uzbekistan, it is stated that the variation can be submitted to the Authority with an urgent variation. The evaluation of variation is provided below.

"The variation (Safety statement BSE/TSE updates) can be added along with the urgent variations later and it is not mandatory to initiate a variation (or an notification) in mean time for this case."

Best Regards,

Bengül BIYIK
International Markets Regulatory Affairs Assistant Specialist
P. 0 312 945 14 36 - ext: 491

genilac.com.tr /gen_ilac
/genilac /genilactr

Attachment # 8b OPS-23-009 ED 05 Jul 23

From: Khrystyna Dunn <Khrystyna.dunn@pharmaxis.com.au>
Sent: Monday, March 6, 2023 3:08 AM
To: Bengül Bıyık <b.biyik@genilac.com>; Ferda Yıldırım Gürsoy <f.gursoy@genilac.com>; 'Liubov Kalmykova' <kalmykova.liubov@gmail.com>; 'e.yambulatova@yandex.ru' <e.yambulatova@yandex.ru>
Cc: Kristen Morgan <Kristen.Morgan@pharmaxis.com.au>; Nadir Ulu <n.ulu@genilac.com>
Subject: Bronchitol - CEP update OPS-23-009

Dear colleagues,

Please be aware that the Lonza/Capsugel's most recent safety statement on BSE (Bovine Spongiform Encephalopathy)/TSE (Transmissible Spongiform Encephalopathy) has been updated and effective from Feb2023 (please find in the attachment).

Please find summary of changes below

Currently submitted CEP V. 2019	Updated as at CEP V. 2022	Comments
Rousselot R1-CEP 2000-029 Rev 05		No Change
Rousselot R1-CEP 2010-043 Rev 00		No Change
Tessenderlo Group R1-CEP 2000-045 Rev 04		No Change
Gelita Group R1-CEP 2001-424 Rev 03		No change
Sterling Gelatin R1-CEP 2001-211 Rev 01		No Change
Nitta Gelatin R1-CEP 2000-344 Rev 03		No Change
Nitta Gelatin R1 CEP 2005-217 Rev 02		No Change
	Pioneer Jellice R1-CEP 2008-048 Rev 00	New CEP

Please let me know if this change require a variation submission in Russia/ Kazakhstan/ Uzbekistan/ Azerbaijan.

Best regards,

Khrystyna Dunn
Regulatory Affairs Associate

pharmaxis

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A: 20 Rodborough Road, Frenchs Forest NSW 2086
www.pharmaxis.com.au

Attachment 9 to OPS - 23-009 KD 24Jul23

Medicines & Healthcare products
Regulatory Agency

10 South Colonnade
Canary Wharf
London
E14 4PU
United Kingdom
gov.uk/mhra

MS. Kristen Morgan
PHARMAXIS EUROPE LIMITED
108 Q HOUSE, FURZE ROAD
SANDYFORD
DUBLIN 18
IE-D18 AY29
IRELAND

21/07/2023

Dear MS. Morgan,

ACCEPTANCE OF GROUPED NOTIFICATION

Our Reference:	PLGB 50608/0002 - 0008
Your Reference:	50608
Product:	Bronchitol 40 mg inhalation powder, hard capsules
Type of Procedure:	National
Submission Type:	Variation
Submission Category:	Type IA
EU Procedure Number (if applicable):	
Territory:	GB
Route:	Direct

The Licensing Authority acknowledges that the Type 1A variation(s) detailed in your application is acceptable. The following change(s) has been notified:

1. To register a change in address for MIAS Pharma Limited from Suite 2, Stafford House, Strand Road, Portmarnock, Co. Dublin, D13H525, Ireland to MIAS Pharma Limited., Suite 1, Stafford House, Strand Road, Portmarnock, Co. Dublin, D13 WC83, Ireland as a batch release site for the finished product.

2. To register the deletion of Arvato Supply Chain Solutions SE., Gottlieb-Daimler Strasse 1, 33428 Harsewinkel, North Rhine-Westphalia, Germany as a batch release and secondary packaging site for the finished product.

Medicines & Healthcare products
Regulatory Agency

3. To register the replacement of Eurofins ams Laboratories Pty Ltd., 8 Rachael Close, Silverwater NSW 2128, Australia with Eurofins ams Laboratories Pty Ltd., 179 Magowar Road
Girraween, NSW 2145, Australia as a QC testing site for the active substance.

4. To register the replacement of Eurofins ams Laboratories Pty Ltd., 8 Rachael Close, Silverwater NSW 2128, Australia with Eurofins ams Laboratories Pty Ltd., 179 Magowar Road, Girraween, NSW 2145, Australia as a QC testing site for the finished product.

5. To register a new TSE Certificate of Suitability, R1-CEP 2008-048-Rev 00, for Gelatin, held by Pioneer Jellice India Private Limited., Revenue Survey No. 65, 66 & 67, Semman Kuppam, Chidambaram Main Road, India-607 005 Cuddalore.

The notification is considered acceptable on the basis of the Marketing Authorisation Holder undertaking that:

i) The notification of change complies with all conditions specified in the guideline on the classification of variations.
ii) All supporting documentation as listed in the guideline on the classification of variations have been provided.
iii) No additional changes have been introduced in this submission apart from the changes proposed in the scope of the above variation.

Failure to comply with any of the above may subsequently deem the notification unacceptable.

Please retain this letter with the formal documents relating to the Marketing Authorisation.

Yours sincerely,

Medicines and Healthcare products Regulatory Agency

Attachment # 10 to OPS-23-009 KD 21 Aug 23

pharmaxis

14th August 2023

Product and Application Business Support (V-PD-BUS)
European Medicines Agency
Domenico Scarlattilaan 6
1083 HS Amsterdam
The Netherlands

Dear Sir/Madam

Bronchitol 40mg inhalation powder, hard capsules (Mannitol)

1*	Applicant/MAH Name	Pharmaxis Europe Limited
2*	Customer Account Number	0000600683 (**only for WS, IG and MAA)**
3*	Customer Reference / Purchase Order Number	Not Applicable
4	INN / Active substance/ATC Code	Mannitol R05CB16
5	Product Name of centrally authorised medicinal product(s)	Bronchitol 40mg inhalation powder hard capsule
5.1*	Nationally Authorised Product(s)	☐
6*	Product Number or Procedure Number or PSUSA (PSUR Single Assessment) Non-EU single assessment PSUR Period Covered (for bot PSUSA and Non-EU procedure)	H XXXX or EMEA/H/C/1252 / IA/XXX/G or PSUSA/000XXXXX/yyyymm ☐ National Marketing Authorisation No -
7*	Submission Type (Please selec)	Grouping of Type IA (IG)
7.1*	Submission Unit Type	Initial
7.2*	Grouping (more than one scope)	☒ Yes
7.3*	Submission Description	Other This Type IA grouped variation consists of the following variations: - 1 X Type IA (Category B.II.d.2.a): to report a minor change to an approved test procedure of the drug product. - 1 X Type IA, Category B.III.1.b.2 – to add a TSE Certificate for an new manufacturer of an excipient for inclusion in Lonza/Capsugel's BSE Declaration

Pharmaxis Europe Limited
108 Q House
Furze Road, Sandyford
Dublin 18, D18AY29
Ireland
T: +353 (0) 1 431 9816
www.pharmaxis.com.au

8*		Please provide the name(s) of any centrally authorised medicinal product for which the same change(s) are being applied for outside of this procedure Product name and number:
9*	RMP included in this submission:	☐ Yes ☒ No RMP version No.
10*	eCTD sequence	0115 Related sequence n/a
11*	Contact Persons' details (include email address)	A) Regarding the content of the submission: Ms Kristen Morgan Telephone number: +61 (0) 2 9454 7257 Fax number (optional): +61 (0) 2 9451 3622 E-mail : kristen.morgan@pharmaxis.com.au B) Regarding eCTD technical questions: Ms. Jenny Bysh Telephone number : +49 (0)89 3585 4018 E-mail : Jenny.Bysh@ndareg.com

To be completed as applicable:

12*	For PAM submissions or in case a procedure such as a variation addresses an outstanding PAM:	☐ I confirm that I have completed the PAM submission form and inserted it in this submission. Please follow this link to access the PAM submission form. ☐ I confirm that the submission does not fall under any categories of the Classification guidance on variations and that the data submitted do not influence the benefit-risk balance and therefore do not require taking further regulatory action on the marketing authorisation. ☐ I confirm that the submission does not include a final study report (except P46 applications)
12.1*	EPITT Number	
13*	For submissions of final study reports in the context of a **variation**	Please select:
14	For P46 submissions	☐study title and number Please select stand alone study(ies). ☐study title and number Please select part of a clinical development program. The Please select application consisting of the full relevant data package (i.e. containing several studies) is expected to be submitted by MM/YY. A line listing of all the concerned studies is attached for your consideration.
15*	Submission in accordance to Art. 8 of Paediatric Regulation (EC) No 1901/2006 of 12/12/2006	Is your product protected by a Supplementary Protection Certificate (SPC) or a patent that qualifies for a SPC? ☐ Yes ☒ No
16	Confirmation that the clinical reports submitted for scientific evaluation are the same as those submitted for publication, in the *Redaction Proposal* and *Final Redacted Versions,* except for the redactions	Included ☐ Yes

This Type IA grouped variation consists of the following two variations:

- A Type IA, Category B.II.d.2.a variation, which serves to report minor changes to an approved test procedure of the drug product – namely to report updates to the analytical procedure for the Determination of Mannitol in Solutions for Aerodynamic Particle Size by LC-MS using Negative Ion Electrospray [TM-028] to reflect use of alternative (Shimadzu) LC-MS instrumentation.

- A Type IA, Category B.III.1.b.2 variation, which serves to provide a TSE Certificate for an new manufacturer of an excipient – namely to add the TSE CEP for Pioneer Jellice's gelatine [R1-CEP 2008-048-Rev 00] for inclusion in Lonza/Capsugel's BSE Declaration as displayed in Module 1.2.5.12 and Module 3.2.R.3.2.

Since both of the two component variations within this submission are of Type IA it is an appropriate situation, in accordance with Article 7(2)(a) of the variation regulation (Commission Regulation (EC) No 1234/2008), to submit these as a Type IA grouping.

For both of the two component variations, all the conditions and documentary requirements have been met (as displayed in Module 1.2 Variation Application Form).

The eCTD sequence (0115) contains the following documents:

- Module 1.0 Cover Letter
- Module 1.0 Cover Letter - Sequence Tracking Table
- Module 1.2 Variation Application Form
- Module 1.2 Variation Form - Annex - present and proposed table
- Module 1.2 Additional - Comparative sample analysis results
- Module 1.2 Annex 5.12 - BSE Declaration from Lonza/Capsugel with updated TSE CEP (updated)
- Module 3.2.P.5.2.6 - Analytical Procedures, Aerodynamic Particle Size Distribution (updated) - updated version of TM-028 provided
- Module 3.2.P.5.3.3 - Validation of Analytical Procedures, Aerodynamic Particle Size Distribution (updated) - reference made to and inclusion of report RN-22-004-01
- Module 3.2.R.3.2 - BSE Declaration from Lonza/Capsugel with updated TSE CEPs (updated)

The MAH can confirm that no other changes have been introduced other than those stated in the Variation Application Form (and its Present and Proposed table) and this cover letter.

The sequence has been submitted via the EMA's Web Client in accordance with the EMA's guidance on dossier requirements for centrally authorised products [EMA/497021/2012 Rev. 26 of 4 January 2021]. This guidance also states that such eCTD format submissions sent to the EMA via the Web Client are considered as being delivered to all National Competent Authorities' representatives, alternates and scientific experts. As such, this sequence is duly delivered to the Rapporteur and Co-Rapporteur, and is available to all remaining CHMP and PRAC members as appropriate.

This submission was virus checked using Security Manager AV Defender. It has been built using DocuBridge 5, to the standards laid out in the current ICH and EU eCTD specifications.

Pharmaxis would be grateful if you could acknowledge receipt of the enclosed documentation. If there are any technical validation issues regarding the eCTD please do not hesitate to contact the technical representative listed in the summary table. Should there be any queries relating to the contact to administrative aspects of this application, please do not hesitate to contact me.

pharmaxis

Yours sincerely,

Kristen Morgan
Pharmaxis
Head of Regulatory Affairs

Tel: +61 (0) 2 9451 7257
Fax: +61 (0) 2 9451 3622

E-mail: kristen.morgan@pharmaxis.com.au

cc:

CHMP members

Attachment 11 to OPS - 23 - 009 KD 21 Aug 23

Khrystyna Dunn

From: Christiane Sievert <csievert@effrx.com>
Sent: Friday, August 18, 2023 8:04 PM
To: Khrystyna Dunn
Cc: Nathalie Véron; Kristen Morgan
Subject: RE: Bronchitol - variation - TSE /BSE updated CEP - gelatin Lonza

Dear Khrystyna,
many thanks for providing the eCTD sequence related to the update of the BSE /TSE CEP related to gelatin from Lonza.
The respective variation is scheduled for submission with Swissmedic by no later than 19.07.2024; based on the EffRx implantation date which is defined to be the Purchase Order date.

Waiting for Plastiape to provide the new MD certificate (before end of 2023), I plan to group these variations.

Kind regards, Christiane

From: Khrystyna Dunn <Khrystyna.dunn@pharmaxis.com.au>
Sent: Wednesday, 16 August 2023 01:59
To: Christiane Sievert <csievert@effrx.com>
Cc: Nathalie Véron <nveron@effrx.com>; Kristen Morgan <Kristen.Morgan@pharmaxis.com.au>
Subject: RE: Bronchitol - variations

Important: External E-Mail

Dear Christiane,

Please find in the attachment the latest sequence 0115 and updated tracking table.

Best regards,

Khrystyna Dunn
Regulatory Affairs Associate

pharmaxis

T: +61421 9338 28 F: +612 9451 3622
A: 20 Rodborough Road, Frenchs Forest NSW 2086
www.pharmaxis.com.au

From: Khrystyna Dunn
Sent: Wednesday, July 26, 2023 2:07 PM
To: 'Christiane Sievert' <csievert@effrx.com>
Cc: Nathalie Véron <nveron@effrx.com>; Kristen Morgan <Kristen.Morgan@pharmaxis.com.au>
Subject: RE: Bronchitol - variations - urgent clarification whether P&L is to be implemented in CH or not

Dear Christiane,

Attachment 12 Page 1 of 2 26 Oct 2023

Sharon Hammond

From: Plani-Lam, Janice <Janice.Plani-Lam@parexel.com>
Sent: Friday, 24 March 2023 1:13 PM
To: Sharon Hammond
Cc: Viana, Ana
Subject: FW: PXS5505-MF-101 - Change in Control of Excipients (CEP) - gelatin capsules - KOR [updated]

Hi Sharon,

Just hear back from both TWN and KOR's regulatory Associate. They confirmed no action require.

With KR,
Janice

From: Yang, Lydia <Lydia.Yang@parexel.com>
Sent: Friday, March 24, 2023 12:15 PM
To: Oh, Jeeyeoun <Jeeyeoun.Oh@parexel.com>; Plani-Lam, Janice <Janice.Plani-Lam@parexel.com>
Cc: Viana, Ana <Ana.Viana@parexel.com>
Subject: RE: PXS5505-MF-101 - Change in Control of Excipients (CEP) - gelatin capsules - KOR [updated]

Hi Jeeyeoun,

Submission in only required for DP (add/delete) and DP manufacturing sites changes. Submission for CMC/IMPD changes not involving IMP's manufacturing site change is not required.

Best Regards,

Lydia Yang
Regulatory Affairs Associate, CORE REGULATORY

Parexel International
t +886-2-2176-9592

Digital Business Card: https://card.link/parexel/items/supHLh

From: Oh, Jeeyeoun <Jeeyeoun.Oh@parexel.com>
Sent: Friday, March 24, 2023 9:09 AM
To: Plani-Lam, Janice <Janice.Plani-Lam@parexel.com>; Yang, Lydia <Lydia.Yang@parexel.com>
Cc: Viana, Ana <Ana.Viana@parexel.com>
Subject: RE: PXS5505-MF-101 - Change in Control of Excipients (CEP) - gelatin capsules - KOR [updated]

Dear Janice,

pharmaxis	FM-378-06	Date Effective: 06-Oct-23	Page 1 of 1

PROGRESS REPORT FOR RAISED QUALITY FORMS

Associated CAR / CR / DR / NCPR / OOS / MTIR / Product Complaint Number: OOS-23-009

Attachment No. 13 **to Associated Document**

Section 1) Progress Report

Written By: Senior QA Officer **Signature & Date:** 03Nov23
(Job Title)

Attachment No.(s): _____ N/A☐

Actions 1, 2, 4 & 5 have been completed.

Remaining actions;

action 3 - Reg. variations have been submitted, all variation approvals have been received except for EU. Submitted in Aug23; ~3months approval.

actions 6 & 7 - updates to ED-21-011-01 and TE-128-01 is in-progress.

Delay in completing remaining actions is considered negligible, TE-178 associated with Aldol Korea product, order for supply in Jan 2024. Template will be updated by end Jan 03Nov23

Updated Proposed Completion Date: Dec 23

Verified By: E. Vaicivgy **Signature & Date:** 03 Nov 23
(Head of Department or Delegate)

Section 2) Update of Applicable Log by QA

Confirm that the applicable log entry has had the proposed completion date updated **Yes ☑; N/A ☐**

Updated By: E. Vaicivgy **Signature & Date:** 03 Nov 23
(Head of Quality or Delegate)