Pfizer Italia S.r.l.
63046 Marino del Tronto (AP) • Via del Commercio, 25/27
Tel. +39 0736 305.111 • Fax +39 0736 305. 263 • www.pfizer.it
Società diretta e coordinata da Pfizer Holding Italy S.p.A.
Stabilimento di Ascoli Piceno

Pfizer Global Manufacturing

Ascoli Piceno, 21 DIC. 2007

TO WHOM IT MAY CONCERN

- **MEDROL 16MG & 32MG TABLETS.**

I, the undersigned, Sylvia Orsini, TSE/BSE Responsible for the pharmaceutical plant Pfizer Italia S.r.l., located in Via del Commercio 25/27, 63046 Marino del Tronto – Ascoli Piceno (Italy), declare the following:

The above mentioned products contain the following ingredients:

• ***Methylprednisolone** (Active ingredient)*	***TSE – Specified risk material***
• Sucrose	TSE – Non specified risk material
• Maize starch	TSE – Non specified risk material
• Lactose	TSE – Non specified risk material
• **Calcium stearate**	***TSE – Specified risk material***
• Liquid paraffin	TSE – Non specified risk material

An extensive TSE/BSE investigation has been performed on the components of the above mentioned products and the "*Specified risk materials*" are:

- **Methylprednisolone** *(Active substance)*
  (Certificate's of Suitability – Nutrient broth: R1-CEP 2000-248-Rev 00, Oleic acid: R1-CEP 2001-079-Rev 00 & Catalase: R1-CEP 2001-168-Rev 00).
- **Calcium stearate**
  (Certificate of Suitability N°: R1-CEP 2000-269-Rev 00 / Stearic acid)

The "Certificate of Suitability" has been issued by the European Directorate for the Quality of Medicines (EDQM), thus meaning that our plant is in full compliance to the TSE Commission Directive 1999/82/EEC. (The above mentioned certificate is attached to this statement).

The Ascoli Piceno Plant is also in full compliance to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMEA/410/01 Rev. 2) which is adopted by the Committee for Proprietary Medicinal Products (CPMP) and by the Committee for Veterinary Medicinal Products (CVMP).

Capitale Sociale € 375.784.800,00 i.v.
Part. IVA 01781570591
Cod. fisc. e Registro Imprese Latina 06954380157
R.E.A. Latina n. 110637
Sede Legale • 04010 Borgo San Michele (Latina) • S.S. 156 Km. 50
Sede Amministrativa • 00188 Roma • via Valbondione, 113

Pharmaceutical grade lactose is scientifically classified as "safe" with regards to BSE. Please find attached our suppliers' Declaration explaining their compliance to the Note for Guidance EMEA/410/01 Rev. 2 which is based on the Public report EMEA/CPMP/BWP/337/02/Public/Final and the Public statement EMEA/CPMP/571/02 (attached).

All the other ingredients are classified as "Non Specified Risk Materials" and therefore do not present risks for TSE/BSE.

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Sylvia Orsini
TSE/BSE Responsible
Site Compliance Department
Ascoli Piceno.

METHYLPREDNISOLONE

Component	Origin of the material (synthetic/ animal/ vegetal)	Country of origin and Tissue used	CEP #
Methylprednisolone			
1. Nutrient broth is used in the fermentation process to generate an early intermediate which is used in the synthesis of drug substance.	1. Animal	1. Australia, Canada and USA Bovine: bile, skeletal muscle, connective tissue, skin, bones free from skulls, spinal cord and vertebrae.	1. R1-CEP 2000-248-Rev 00
2. Oleic acid is used as stating material for a reagent (Polysorbate 80) used in the master cell bank and working cell bank and during the bioconversion of an early intermediate, used in the synthesis of drug substance.	2. Animal	2. USA and Canada Tallow	2. R1-CEP 2001-079-Rev 00
3. Catalase is used in the fermentation process to generate an early intermediate which is used in the synthesis of drug substance.	3. Animal	3. USA Bovine, liver	3. R1-CEP 2001-168-Rev 00
4. Lard oil is used in the fermentation process to produce a precursor to the starting material for the active substance	4. Animal	4. USA Porcine	4. N/A
5. Soy flour hydrolyzate is used in the fermentation process to generate an early intermediate which is used in the synthesis of drug substance.	5. Animal	5. USA and Canada Porcine	5. N/A
6. Edamin S is used in the fermentation process to generate an early intermediate which is used in the synthesis of drug substance.	6. Edamin S	6. USA and Canada, Porcine, Pancreas; USA, Australia and New Zealand, Bovine, milk	6. N/A

An extensive TSE/BSE assessment has been performed on Methylprednisolone as described in the *Joint CPMP/CVMP Note for Guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human or veterinary medicinal products - EMEA 410/01Revision 02.*

The Certificates of Suitability for Nutrient broth, Oleic acid and Catalase have been issued by the European Directorate for the Quality of Medicines and attached hereafter.

Lard oil and soy flour hydrolyzate are from porcine origin and to date porcine species have not been reported to be susceptible to transmissible spongiform encephalopathy and are out of the scope of the Guideline mentioned above.

The Edamin S is manufactured from milk taken from healthy animals, in the same conditions as milk collected for human consumption. No other product from ruminant origin has been used to prepare the lactose except calf rennet. The calf rennet is in compliance with the requirements defined in Regulation 999/2001 and other applicable EU legislation. No other product from ruminant origin has been used to prepare the Edamin.

edqm

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

European Directorate for the Quality of Medicines
Division Certification of Substances

Certificate of suitability
No. R1-CEP 2000-248-Rev 00

Name of the substance:
NUTRIENT BROTH
(codes 231000, 232000, 233000 and 234000)

Name of holder:
BECTON, DICKINSON AND COMPANY
7 Loveton Circle
USA - 21152 Sparks, Maryland

Sites of production:
BECTON, DICKINSON AND COMPANY
39 Loveton Circle
USA - 21152 Sparks, Maryland

BECTON, DICKINSON AND COMPANY
920 Henry Street
USA - 48201 Detroit, Michigan

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R0-CEP 2000-248-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 sites of production mentioned above, USA - 21152 Sparks, Maryland and USA - 48201 Detroit, Michigan, we certify that the substance NUTRIENT BROTH 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:	Australia, Canada and United States of America
- nature of animal tissues used in manufacture:	Bovine bile, bovine skeletal muscle, bovine connective tissue, bovine skin, and bovine bones free from skulls, spinal cord and vertebrae

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.

Postal Address: 226 Avenue de Colmar (entrance rue Schertz) B.P. 907 — F 67029 Strasbourg Cedex 1
Telephone: 03.88.41.30 30 - Fax 03.88.41.27.71 – Web site : http://www.pheur.org

Manufacture of the substance shall take place in accordance with a suitable quality assurance system such as ISO 9001 and GMP, 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 **1 October 2006** 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 40 lines only.

Dr. A. ARTIGES
Director of the Quality of Medicines

Strasbourg, 3 October 2006

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

BECTON, DICKINSON AND COMPANY, as holder of the certificate of suitability

R1-CEP 2000-248-Rev 00 for NUTRIENT BROTH

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)*

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)*:

Postal Address: 226 Avenue de Colmar (entrance rue Schertz) B.P. 907 – F 67029 Strasbourg Cedex 1
Telephone: 03.88.41.30 30 - Fax 03.88.41.27.71 - Web site : http://www.pheur.org

edqm

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

European Directorate for the Quality of Medicines
Certification Unit

Certificate of suitability
No. R1-CEP 2001-168-Rev 00

Name of the substance:
CATALASE
Product No C9322

Name of holder:
SIGMA-ALDRICH CORPORATION
3050 Spruce Street
USA – 63103 Saint Louis, Missouri

Site of production:
SIGMA-ALDRICH CORPORATION
3500 Dekalb Street
USA – 63118 Saint Louis, Missouri

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R0-CEP 2001-168-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 of production mentioned above, USA – 63118 Saint Louis, Missouri, we certify that the substance CATALASE 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: New Zealand
- nature of animal tissues used in manufacture: Bovine liver

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 such as ISO 9001, 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.

Postal Address: 226 Avenue de Colmar (entrance rue Schertz) B.P. 907 — F 67029 Strasbourg Cedex 1
Telephone: 03.88.41.30 30 - Fax 03.88.41.27.71 – Web site : http://www.pheur.org

This certificate is renewed from **11 June 2006** 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 33 lines only.

Dr. A. ARTIGES
Director of the Quality of Medicines

Strasbourg, 12 May 2006

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

SIGMA-ALDRICH CORPORATION, as holder of the certificate of suitability

R1-CEP 2001-168-Rev 00 for CATALASE

hereby authorises Pfizer
(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)*

Unknown

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*): Mike Shannon 05/19/06

Postal Address: 226 Avenue de Colmar (entrance rue Schertz) B.P. 907 — F 67029 Strasbourg Cedex 1
Telephone: 03.88.41.30 30 - Fax 03.88.41.27.71 - Web site : http://www.pheur.org

European Directorate for the Quality of Medicines
Division Certification of Substances

Certificate of suitability
No. R1-CEP 2001-079-Rev 00

Name of the substance:
OLEIC ACID
Uniqema Chicago (USA)

Name of holder:
UNIQEMA
4650 South Racine Avenue
USA - IL 60609-3321 Chicago

Site of production:
UNIQEMA
4650 South Racine Avenue
USA - IL 60609-3321 Chicago

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R0-CEP 2001-079-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 of production mentioned above, USA - IL 60609-3321 Chicago, we certify that the substance OLEIC ACID 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.

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 such as ISO 9001, 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.

Postal Address: 226 Avenue de Colmar (entrance rue Schertz) B.P. 907 – F 67029 Strasbourg Cedex 1
Telephone: 03.88.41.30 30 - Fax 03.88.41.27.71 – Web site : http://www.pheur.org

This certificate is renewed from **25 January 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 31 lines only.

Dr. A. ARTIGES
Director of the Quality of Medicines

Strasbourg, 10 January 2007

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

UNIQEMA, as holder of the certificate of suitability

R1-CEP 2001-079-Rev 00 for OLEIC ACID

hereby authorises Pfizer
(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 TWEEN® 80 Polysorbate 80 NF

********** Products Not Specified **********

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*):
25-Jan-2007

Postal Address: 226 Avenue de Colmar (entrance rue Schertz) B.P. 907 — F 67029 Strasbourg Cedex 1
Telephone: 03.88.41.30 30 - Fax 03.88.41.27.71 - Web site : http://www.pheur.org