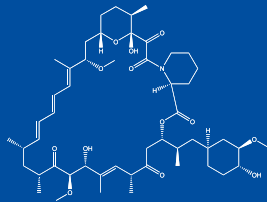




Oskar Tropitzsch



Facts on Rapamycin Rapamycin-Ethanol-Solution

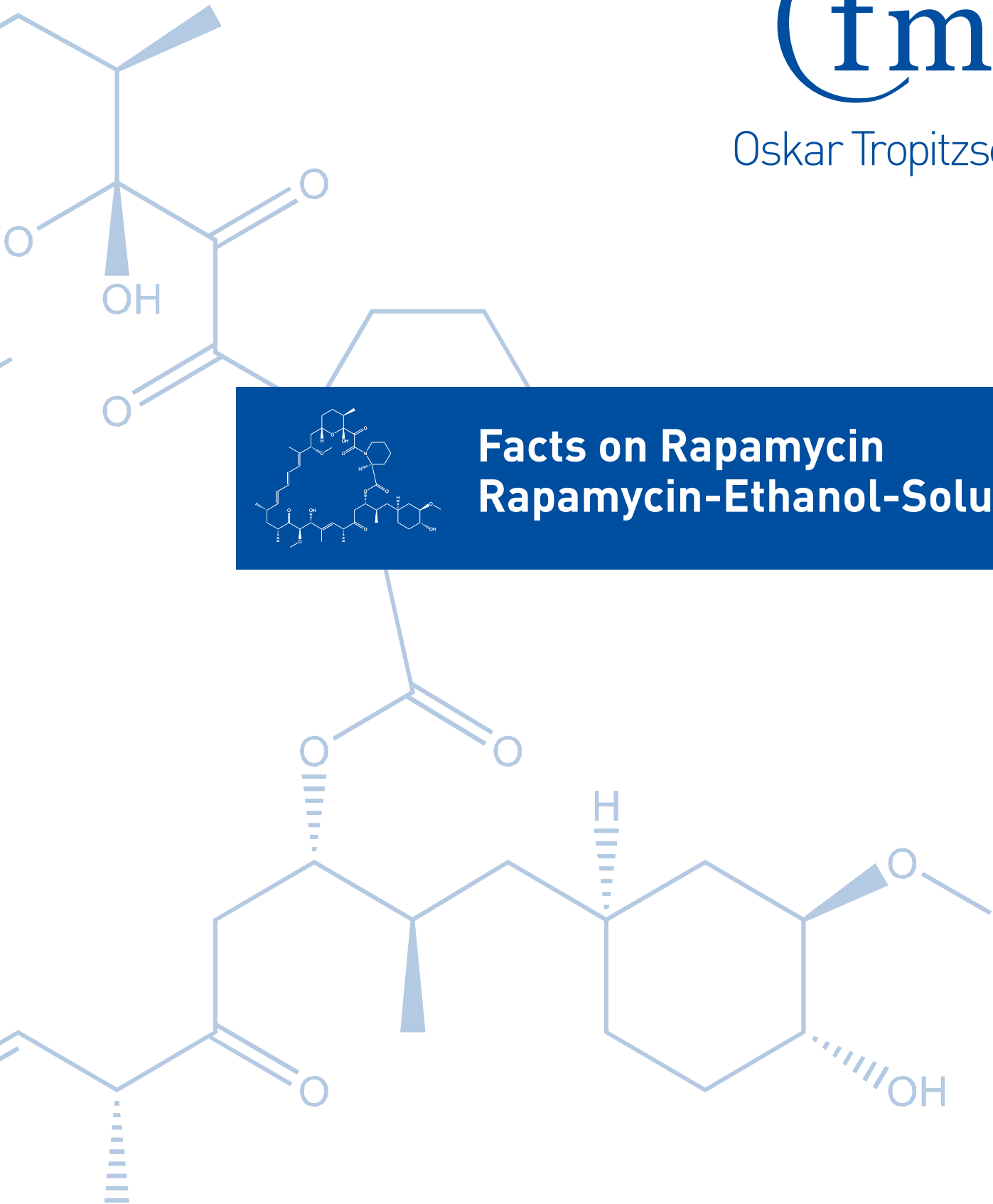




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	Rapamycin-Ethanol-Solution order procedure	8
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Where can Rapamycin, the Rapamycin-Ethanol-Solution be ordered?

The manufacturer of the Rapamycin-Ethanol Solution is:

Marien-Pharmacy
Kolpingstraße 2
D-95615 Marktredwitz
Germany

Phone.: +49 (0) 9231 51 60
Fax.: +49 (0) 9231 636 40
Email: info@ma-m.de
Website: www.ma-m.de

Person in charge: Mr. Bauer, Pharmacist

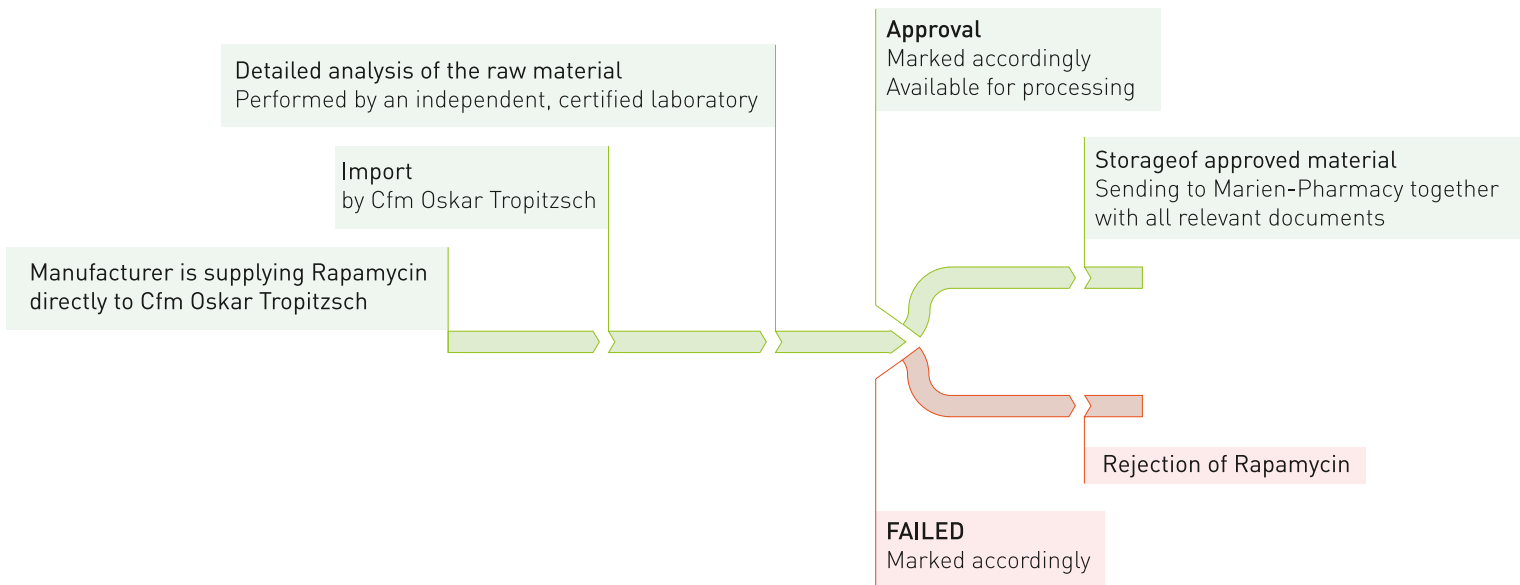
Accounting, logistics and quality control are managed by:

Cfm Oskar Tropitzsch e.K.
Waldershofer Str. 51
D-95615 Marktredwitz
Germany

Phone.: +49 (0) 9231 96 19 24
Fax: +49 (0) 9231 96 19 60
Email: info@cfmot.de
Website: www.cfmot.de

Person in charge: Mr. Schaeffler

Detailed raw material pathway



Which Certificates are available

Cfm Oskar Tropitzsch:

Supply of Active Pharmaceutical Ingredients acc. §67 AMG. Supervision confirmation according to §64 ff. AMG by the government of Upper Franconia, Bavaria, Germany

AMG stands for German medicine law.
The Government of Upper Franconia, Bavaria Germany confirms, that Cfm Oskar Tropitzsch is authorised according to § 67 AMG to sell/purchase/trade API's.

Regierung von Oberfranken



Regierung von Oberfranken, Postfach 110165, 95420 Bayreuth

Firma
Cfm Oskar Tropitzsch
Waldershofer Str. 49 - 51
95615 Marktredwitz

Ihre Zeichen / Ihre Nachricht vom	Bitte bei Antwort angeben Unser Zeichen / Ansprechpartner	Telefon / Fax / Zimmer-Nr. / E-Mail	Bayreuth
05.01.2010 Frau Carina Zintl	53.2-2672 Herr Wölfel	Telefon (0921) 604 – 1920 Fax (0921) 604 – 4920 Zimmer-Nr. K 007 gerhard.woelfel@reg-ofr.bayern.de	19.02.2010

Arzneimittelgesetz (AMG); Überwachung des Verkehrs mit Arzneimitteln und Wirkstoffen

Sehr geehrte Damen und Herren,

für das Inverkehrbringen und den sonstigen Handel mit Wirkstoffen besteht nach § 67 AMG eine allgemeine Anzeigepflicht.

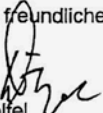
Hiermit wir bestätigt, dass die Firma

Cfm Oskar Tropitzsch
Waldershofer Str. 49 - 51
95615 Marktredwitz

den Handel mit Wirkstoffen bei der zuständigen Regierung von Oberfranken ordnungsgemäß angezeigt hat.

Die Firma unterliegt nach §§ 64ff AMG der arzneimittelrechtlichen Überwachung durch uns.

Mit freundlichen Grüßen


Wölfel
Pharmaziedirektor

Hauptgebäude
Ludwigsstraße 20
95444 Bayreuth
Stadtbus Linie 14
Haltestelle Stierplatz

Telefon (0921)604-0
Telefax (0921)604-1258
E-Mail poststelle@reg-ofr.bayern.de
Internet
<http://www.regierung.oberfranken.bayern.de>

Besuchszeiten
Mo-Do: 08:00 - 12:00 Uhr
13:00 - 15:30 Uhr
Fr: 08:00 - 12:00 Uhr
oder nach Vereinbarung

Kontoführende Stelle
StOK Bayern in Landshut
Kto.-Nr. 743 015 30
BLZ 750 000 00
Dt. Bundesbank Regensburg



Marien-Pharmacy:

DIN-EN ISO 9001:2008

DIN-EN ISO 14001:2005

All other necessary certificates for a pharmacy.

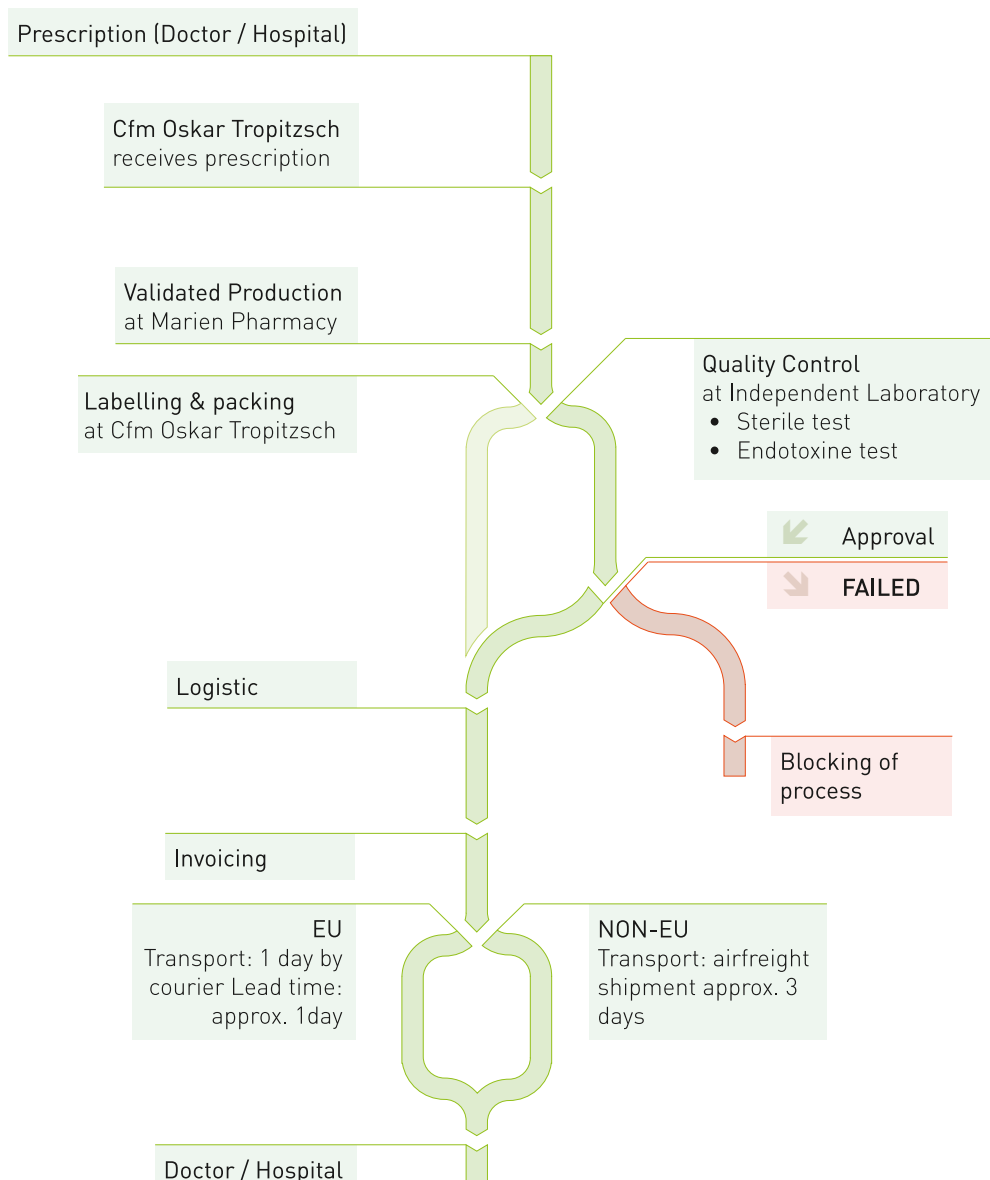
Example Certificates are enclosed.



Detailed order process

1. Original-prescription with number of vials, volume, concentration and application is necessary and has to be send in **original** to Cfm Oskar Tropitzsch e.K. Example enclosed.
2. For EU: maximal 100 vials can be ordered at once.
3. For customers outside EU: no limitation
4. Price list is available, please contact Cfm Oskar Tropitzsch e.K.

Rapamycin-Ethanol-Solution order procedure



Quality Control

Each Rapamycin raw material batch is analysed at an independent laboratory. Only after approval this raw material is used for the production of the Rapamycin-Ethanol-Solution.

Each Rapamycin-Ethanol-Batch is going to be sent to an external laboratory for a sterility test.

Frequently, Limulus-, Endotoxin- und Assay-Tests are performed at an independent laboratory.

The solution is produced based on a validated manufacturing process.



Chemisches Laboratorium Dr. Hermann Ulex Nachf.

Stammhaus gegr. Andreae 1763 als "Apputecke am Stubbenhuk" am Orde des Brauerknechtgrabens

Inhaber: Hans-Joachim Mierendorff

Royal Soc.f.Food a.Drug Res.London/Glasgow (RSFDR) • Intern.Soc.f. Residue-Anal.Wash.,D.C./Palo Alto C.A. (ISRA)
European Federation for the Science and Technology of Lipids (EFL) / Deutsche Ges. f. Fettw. e.V. Münster / Westf.(DGF)

Chem. Laboratorium Dr.H.Ulex Nachf., Glasmoorstr.23, 22851 Norderstedt

Chemisches Handelslaboratorium
Meßstelle für Radioaktivität
Accreditation EN 17025 in Progress

Firma
CFM-Oskar Tropitzsch
PF 568

Example

95605 Marktredwitz

Glasmoorstraße 23
22851 Hamburg-Norderstedt
Tel. : +49-40-529 587- 0
Fax : +49-40-529 587-33
Mobil: +49-172-655 73 10
eMail: service@ulexlab.de
Internet: www.ulexlab.de

Hamburg-Norderstedt,
den

Certificate of Analysis No. 5X 26 02

Rapamycin Ethanol-Solution
Cfm – Oskar Tropitzsch
1mL 20mg/mL steril
Light protected storage at 2-8°C
Ch. 94116901-HS
retest
Marienapotheke, 95615 Marktredwitz

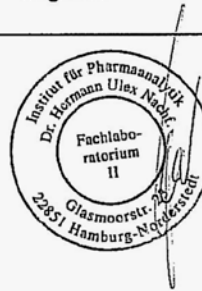
We have got the above sample for analysing for sterility by the method:

Sterility of parenteral pharmaceuticals acc. to EP2.6.1, EP IV.08.

The analysis was made by our contracted microbiological laboratory during 14 days.

Result:

Aerobe	35°C : after 14 days:	no growth
Anaerobe	35°C : after 14 days	no growth
Fungi	20°C : after 14 days	no growth



C:\Office52\user\TX\Pharma\Rapamycin\CFM5X2602engl.sdw

Fachlaboratorium I:
Allgemeines Handelslaboratorium

Lebensmittel, Gewürze, Genussmittel, Fette, Öle,
Futtermittel, Düngemittel, Trinkwasser, Abwasser,
Kosmetika, Bedarfsgegenstände,
Betriebsberatung, laufende Kontrollen, Probe-
nahmen, lebensmittelrechtliche Beratung

Fachlaboratorium II:
Industrie und
Pharmalaboratorium
Drogen, Chemikalien,
Arzneibuchwaren, Zuberei-
tungen, Pharmaforschung und
Entwicklung

Fachlaboratorium III:
Institut für Umwelt- und Rückstandsanalytik

Mikro- und Ultramikroanalytik von Pflanzenschutzmittelrückständen (Pesticiden),
Cancerogenen, toxischen Schwermetallen, Mycotoxinen (Aflatoxine), Giften etc.,
Aminosäurespektren, enzymatische Analysen.
Dünnschicht-, Säulen- und Gaschromatographie, Gelchromatographie, HPLC, UV-, IR-
und Fluoreszenzspektrophotometrie, Atomabsorptionsspektroskopie (Hydrid-,
Flammen- und Graphitrohr-AAS), Polarographie, Elektrophorese etc.

Gerichtsstand und Erfüllungsort: Hamburg. Die in der 9. Auflage des Allgemeinen deutschen Gebührenverzeichnisses für Chemiker abgedruckten allgemeinen Vertragsbedingungen,
insbesondere § 10, werden ausdrücklich zum Vertragsinhalt erhoben. Restmuster stehen, soweit möglich, 30 Tage zur Verfügung.

HRA 43 936 AG. Hamburg

USL-ID Nr.: DE 134 361 103

Example of a Steril-test certificate

Chemisches Laboratorium Dr. Hermann Ulex Nachf.

Stammhaus gegr. Andreae 1763 als "Apputecke am Stubbenhuk" am Orde des Brauerknechtgrabens

Inhaber: Hans-Joachim Mierendorff

Royal Soc.f.Food a.Drug Res.London/Glasgow (RSFDR) • Intern.Soc.f. Residue-Anal.Wash.,D.C./Palo Alto C.A. (ISRA)
European Federation for the Science and Technology of Lipids (EFL) / Deutsche Ges.f.Fettw.e.V. Münster / Westf.(DGF)

Chem. Laboratorium Dr.H.Ulex Nachf., Glasmoorstr.23, 22851 Norderstedt

Firma
CFM-Oskar Tropitzsch
PF 568

95605 Marktredwitz

Example

Chemisches Handelslaboratorium
Meßstelle für Radioaktivität
Accreditation EN 17025 in Progress

Glasmoorstraße 23
22851 Hamburg-Norderstedt

Tel. : +49-40-529 587- 0

Fax : +49-40-529 587-33

Mobil: +49-172-655 73 10

eMail: service@ulexlab.de

Internet: www.ulexlab.de

Hamburg-Norderstedt,
den

Certificate of Analysis No. 5Z 09 01 B

Rapamycin Ethanol-Solution
Cfm – Oskar Tropitzsch
2,5mL 20mg/mL steril
Light protected storage at 2-8°C
Ch. 94116905-TK
retest
Marienapotheke, 95615 Marktredwitz

We have got the above sample for analysing for Endotoxines by the method:

„Prüfung der Bakterien-Endotoxine bei
parenteralen Arzneimitteln nach EP 2.6.14“

The analysis was made by our contracted microbiological laboratory.

We got the following result:

Content of Endotoxines: <0,03 E.U. /mL (D.L.)

The solution is free of Endotoxine

(Maßgeblich für den Inhalt und die Richtigkeit dieses ins Englische übersetzten Untersuchungsberichtes ist allein der deutsche Urtext.)

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Fachlaboratorium I
Allgemeines Handelslaboratorium
Lebensmittel, Gewürze, Genußmittel, Fette, Öle,
Futtermittel, Düngemittel, Trinkwasser, Abwasser,
Kosmetika, Bedarfsgegenstände,
Betriebsberatung, laufende Kontrollen, Probe-
nahmen, lebensmittelrechtliche Beratung

Fachlaboratorium II:
Industrie und
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Drogen, Chemikalien,
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Mikro- und Ultramikroanalytik von Pflanzenschutzmittelrückständen (Pesticiden),
Carcinogenen, toxischen Schwermetallen, Mycotoxinen (Aflatoxine), Giften etc.,
Aminosäurespektren, enzymatische Analysen,
Dünnschicht-, Säulen- und Gaschromatographie, Gelelektrophorese, HPLC, UV-, IR-
und Fluoreszenzspektrophotometrie, Atomabsorptionsspektroskopie (Hydrid-,
Flammen- und Graphitrohr-AAS), Polarographie, Elektrophorese etc.

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insbesondere § 10, werden ausdrücklich zum Vertragsinhalt erhoben. Restmuster stehen, soweit möglich, 30 Tage zur Verfügung.

HRA 43 936 AG. Hamburg

UST-ID Nr.: DE 134 361 103

Example of an Endotoxin-test certificate

Certificate of Analysis **Example**

Product:	Rapamycin (Sirolimus)
Code-Number:	53123-88-9/
CAS-Number:	53123-88-9
Formula:	C ₅₁ H ₇₉ N ₀₁₃
Formula weight:	914,19 g/mol
Manufacturing Date:	...
Expiry Date:	...
Storage	+2/+8°C

Test	Specifications	Results
Batch	
Appearance	white to off-white powder	White powder
Identification	Corresponds to the standard	Conforms
HPLC Retention time		
FT-IR	Complies with the reference standard	Conforms
Specific rotation	-140° to -160° on anhydrous basis	-151°
Water (K.F.)	NMT 1.0%	0.2%
Residue on Ignition	NMT 0.2%	0.16%
Heavy metal	NMT 20ppm	NMT 20ppm
Chromatographic purity		
Individual specified impurity	NMT 0.30% (Area%)	
IP A (RRT = 0.7)		0.27%
IP B (RRT = 0.8)		0.08%
IP C (RRT = 0.9)		0.13%
IP D (RRT = 1.16)		0.01%
IP E (RRT = 1.2)		0.06%
IP F (RRT = 1.3)		0.08%
Individual unspecified impurity	NMT 0.10% /Area%	Not detected
Total impurities	NMT 2.0% (Area%)	0.62%
Assay (W/W, anhydrous basis)	98.0%-101%	99.3%
Residual solvents		
Methanol	NMT 3000 ppm	LT 100 ppm
Ethyl acetate	NMT 5000 ppm	LT 100 ppm
Acetone	NMT 5000 ppm	LT 100 ppm
N-Hexane	NMT 290 ppm	LT 100 ppm
Isopropyl ether	NMT 4000 ppm	531 ppm

Data as received from supplier

Handwritten signature

HPLC chart is available on request

Rapamycin additional information

Sirolimus is a relatively new immunosuppressant drug used to prevent rejection in organ transplantation, and is especially useful in kidney transplants. It is also known as rapamycin. Sirolimus is a macrolide antibiotic („-mycin“) first discovered as a product of the bacterium *Streptomyces hygroscopicus* in a soil sample from an island called Rapa Nui, better known as Easter Island. It is marketed as Rapamune® by Wyeth.

Interestingly, rapamycin originally was developed as an antifungal agent. However, this was abandoned when it was discovered that rapamycin had potent immunosuppressive and antiproliferative properties.

Mechanism of action

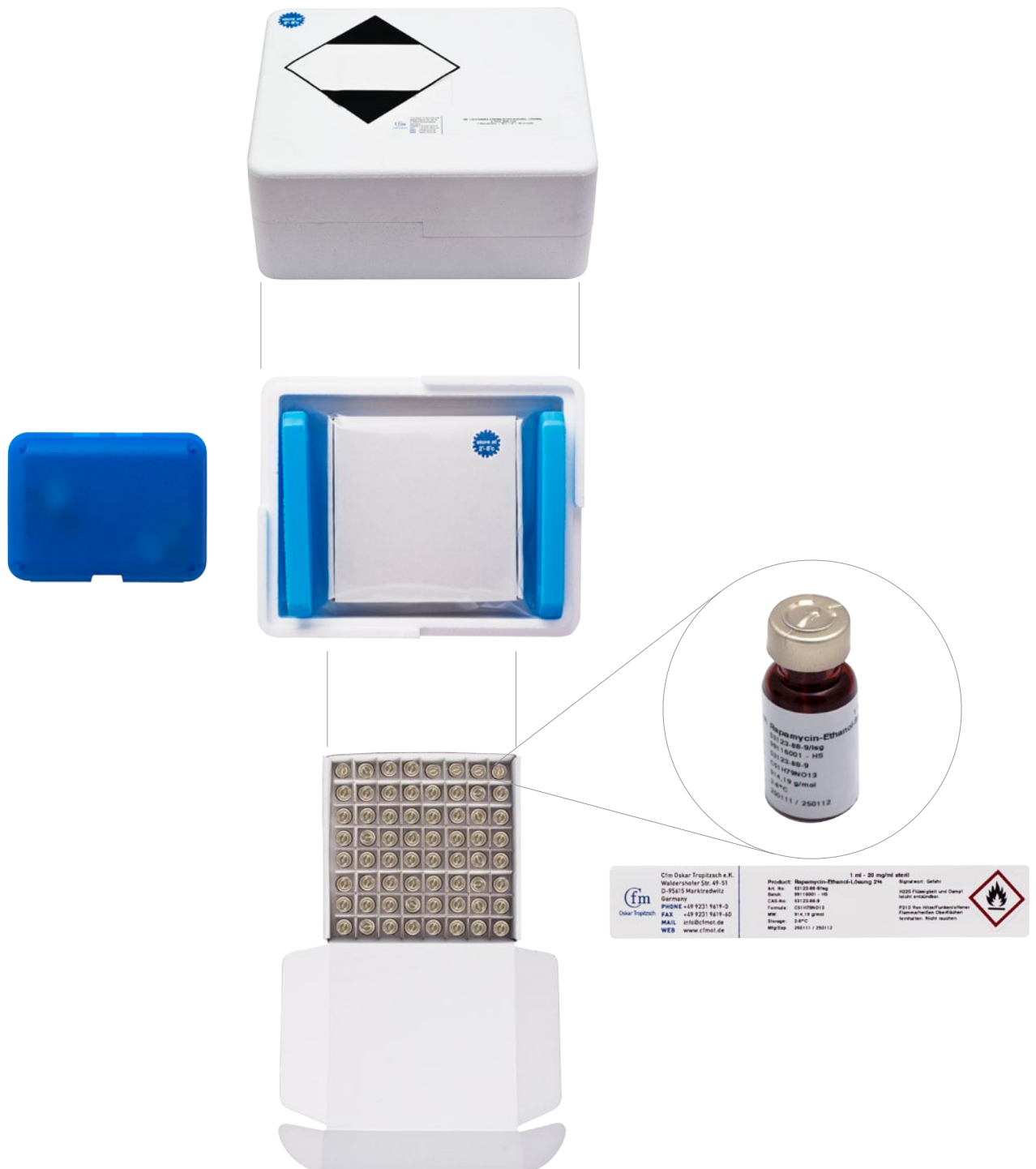
Despite its similar name, it is not a calcineurin inhibitor like tacrolimus or ciclosporin. However, it has a similar suppressive effect on the immune system. Sirolimus inhibits the response to IL-2 and thereby blocks activation of T- and B-cells. In contrast, tacrolimus and cyclosporine inhibit the production of IL-2.

The mode of action of sirolimus is that it binds to the cytosolic protein FK-binding protein 12 (FKBP12), in a similar way to tacrolimus. However, unlike the tacrolimus-FKBP12 complex which inhibits calcineurin (PP2B), the sirolimus-FKBP12 complex inhibits the mammalian target of rapamycin (mTOR) pathway through derepression of PP2A, resulting in inhibition of lymphocyte proliferation.

Anti-proliferative effects

The anti-proliferative effect of sirolimus has also been used in conjunction with coronary stents to prevent restenosis in coronary arteries following balloon angioplasty. The sirolimus is formulated in a polymer-free coating that affords controlled release through the healing period following coronary intervention. Several large clinical studies have demonstrated lower restenosis rates in patients treated with sirolimus eluting stents when compared to bare metal stents, resulting in fewer repeat procedures.

Packaging Details



Abbreviations and Common Terms

Abbreviation	Definition
API	A ctive P harmaceutical I ngredient
ASMF	A ctive S ubstance M aster F ile
Assay	Content (Purity)
BfArM	Federal Institute for Drugs and Medical Devices (Germany)
cGMP	C urrent G ood M anufacturing P ractice
C of A - CoA	C ertificate of A nalysis
DMF	D rug M aster F ile (old name – Now ASMF)
E.U.	E ndotoxin U nit (related to the limulus test)
FDA	F ood and D rug A dministration (USA)
FT-IR	F ourier T ransform I nfrared Spectroscopy
HPLC	H igh P erformance L iquid C hromatography (Analysis Method)
IP	I mpurity (derivatives or not classified compounds)
ISO	I nternational S tandards O rganisation
Limulus test	Is also named Endotoxin test
M.P.	M elting P oint
NMT	N ot M ore T han (Maximum value)
Ph. EUR	E uropean P harmacopoeia
PPM	P arts P er M illion
Residue on Ignition	Ash content
UV VIS	U ltraviolet- V isible Spectroscopy (Quantitative analysis method)
Water (K.F.)	Water content according to Karl Fisher (Method of Analysis)
Vial	In our case a brown glass vial

SINCE 1788 - FROM ALCHEMY TO LIFE SCIENCE
220 years
Chemicals for Mankind



Oskar Tropitzsch

Cfm Oskar Tropitzsch e.K.
Waldershofer Str. 49-51
95615 Marktredwitz
Germany

PHONE +49 (0) 92 31 96 19-0
FAX +49 (0) 92 31 96 19-60
EMAIL info@cfmot.de
WEBSITE www.cfmot.de

Trade register: Amtsgericht Hof HRA 2646
Tax number: 258/281/70123
VAT-Id-Nr. DE 134208061
Holder Dipl.-Kfm. Oskar Tropitzsch

