Algemene gegevens / General Information

Programma / Programme	:	**COVID-19 Programma**
Subsidieronde / Subsidy round	:	**Bottom-up ronde COVID-19 aandachtsgebied 1**
Projecttitel / Project title	:	**Fetal cells to save adult lives – umbilical cord derived mesenchymal stromal cells in critical COVID-19 patients**
Projecttaal / Project language	:	**Engels / English**
Geplande startdatum / Planned start date	:	**30-07-2020**
Geplande duur / Planned duration	:	**24 maanden / months**
Datum indienen / Date of application	:	**14-05-2020**
Projecttype / Project type	:	**Toegepast onderzoek**
Vervolg eerder ZonMw-project / Continuation previously funded project ZonMw	:	**Nee / No**

Projectleden / Project members

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Technical University Dresden
University Hospital Carl Gustav Carus
Neonatology
Fetscherstraße 74
01307 DRESDEN

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5.1.2e 1.2e
Functie / Position: 5.1.2e *Opleiding / Education:*
Studierichting / Subject:
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Projectgegevens / Project information

Aandachtsgebieden / Focus

1.1 Thema's aandachtsgebied 1
- Behandeling
- Virus, immuniteit, immuunrespons en pathogenese

1.3 Setting
- Ziekenhuiszorg

Samenvatting / Summary

RESEARCH QUESTION
COVID-19 represents a major threat to societies and their health care systems. Two major pathways seem to be pivotal to cause life threatening damage; severe systemic inflammation and damage to the pulmonary endothelium leading to pulmonary thrombosis. Our study group have the unique availability of GMP approved and ready for use fetal cells, non-invasively derived from umbilical cords. These umbilical cord derived mesenchymal stromal cells (UC-MSC) have both a very potent anti-inflammatory activity and a favorable effect on the pulmonary endothelium. Therefore, UC-MSC are a highly interesting cell therapy to save critical COVID-19 patients.

Our main research questions are whether it is safe and if it is feasible to administer UC-MSC to critical COVID-19 patients at the ICU. We also aim to find prognostic biomarkers for patient selection and disease progression.

URGENCY
Due to the high risk associated with COVID-19 respiratory insufficiency, there is an overall consensus to find an effective intervention as quick as possible. Furthermore, COVID-19 patients burden ICU capacity and have hampered regular care. Reducing duration of mechanical ventilation and improving survival would reduce the impact of COVID-19 on the ICU capacity, enabling full restart of regular interventions.

HYPOTHESIS
We hypothesize that UC-MSC therapy is safe and will reduce respiratory symptoms and improve outcome in critical COVID-19 patients.

APPROACH

We will perform a phase-I dose seeking and subsequent phase-II feasibility study of UC-MSC in critical COVID-19 patients. In the phase-I study we will use dose-escalation, monitoring dose limiting toxicity. The highest tolerable dose will be taken forward into a phase-II feasibility study with primary outcome mechanical ventilation days and alive after 28 days. We would consider a reduction of 4 ventilation days a sufficient success to take UC-MSC therapy forward into a phase-III international randomized controlled trial.

Trefwoorden / Keywords
COVID-19; beademing; intensive care; mesenchymale stromale cellen; cel therapie; endotheelschade; pulmonale trombose; systemische inflammatie

Samenwerking / Collaboration

Samenwerking tussen onderzoek en praktijk / Cooperation between research and practice:
Nee / No

Inhoud / Content

Disciplines / Disciplines

- Longziekten / Pulmonology
- Infecties, parasitologie, virologie / Infections, parasitology, virology

Financiële gegevens / Financial data

ZonMw budget

	Jaar / Year								
Kostenpost	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	**Totaal / Total**
Personeel	5.1.1c								200.000
Materieel									250.000
Implementatie									25.000
Apparatuur									0
Overig									25.000
Totaal / Total	**237.500**	**262.500**	**0**	**0**	**0**	**0**	**0**	**0**	**500.000**

Co-financiering / Cofinancing

Naam co-financier / Name of cofinancier	Bedrag / Amount	Status

Bijzondere gegevens / Additional information

Vergunningen / Permits

	Verklaring nodig / Statement required?		Status verklaring / Statement status		
	Ja / Yes	Nee / No	Verkregen / Acquired	Aangevraagd / Applied	Nog niet aangevraagd / Not applied yet
METC	X				X
DEC		X			
WBO		X			

Onderschrijvingen / Assents

	Ja / Yes	Nee / No	N.v.t. / N.A.
Code biosecurity / Code Biosecurity			X
Code openheid dierproeven / Code Transparency of Animal Testing			X

Andere vergunningen / Other permits

METC goedkeuring noodzakelijk - dossier wordt momenteel opgebouwd - verwachte submissie eind mei 2020.

AANVRAAGFORMULIER PROJECTIDEE – BOTTOM-UP RONDE

COVID 19 programma

Deadline voor indiening: 14 mei 2020 (14:00 u)

LEES ALSTUBLIEFT ALLE INSTRUCTIES IN BIJLAGE ''TOELICHTING INDIENING PROJECTIDEE'' VAN DE OPROEPTEKST ZORGVULDIG!

Wanneer u het formulier heeft ingevuld:

1. **Zet het formulier om naar een PDF file en controleer de details**
2. **Upload het complete formulier als een bijlage bij uw indiening in Projectnet (Let op: dit zijn twee verschillende links, gebruik maar 1 van de 2!)**

ProjectNet: Aandachtsgebied 1 (voorspellende diagnostiek en behandeling)
ProjectNet: Aandachtsgebied 2 (zorg en preventie)

BASISGEGEVENS (voorpagina)

NAAM VAN DE HOOFDAANVRAGER:

5.1.2e

ORGANISATIE:

Erasmus Medical Center, Rotterdam, The Netherlands

PROJECTTITEL:

Fetal cells to save adult lives – umbilical cord derived mesenchymal stromal cells in critical COVID-19 patients

DATASTEWARD:

Wie is de datasteward die de open science en FAIR data planning in uw project ondersteunt? Zie de webinars op de ZonMw website om de datastewards te informeren en ondersteunen.

☒ Ik betrek een datasteward bij mijn project:
Naam: 5.1.2e
Instituut: Erasmus Medisch Centrum, Research Suite
E-mail: 5.1.2e @erasmusmc.nl
Was aanwezig bij de webinar: ☒ Ja ☐ Nee

ONDERZOEKSVOORSTEL **max 3 pagina's A4** (inclusief literatuurreferenties)	(voorpagina met basisgegevens niet meegerekend - font type Arial 10 pts)

1. PROBLEEMSTELLING EN DOELSTELLING(EN):

COVID-19, the disease caused by infection with the pandemic SARS-CoV-2, represents a major threat to societies and their health care systems. Many patients suffering from COVID-19 require intensive care due to respiratory insufficiency, which is the main cause of mortality in patients admitted to the intensive care unit (ICU)[1]. In the Erasmus Medical Center, the mortality of ICU-admitted patients is 30-35% and the mean duration of ICU stay is 22 days, which burdens ICU capacity significantly [personal data]. Current therapeutic approaches include aggressive standard supportive care and treatment of any other co-infections. Therapeutic options are lacking and **new therapies are urgently needed**. Due to our already established international collaboration, a high potential innovative therapy derived from fetal cells, **umbilical cord derived mesenchymal stromal cells** (UC-MSC), is readily available in our center.

Two major pathways seem to be responsible for COVID-19 induced damage and related critical respiratory distress; (1) **systemic inflammation** leading to cytokine release storms (CRS) and (2) inflammation induced **endothelial damage leading to pulmonary thrombosis**[2].

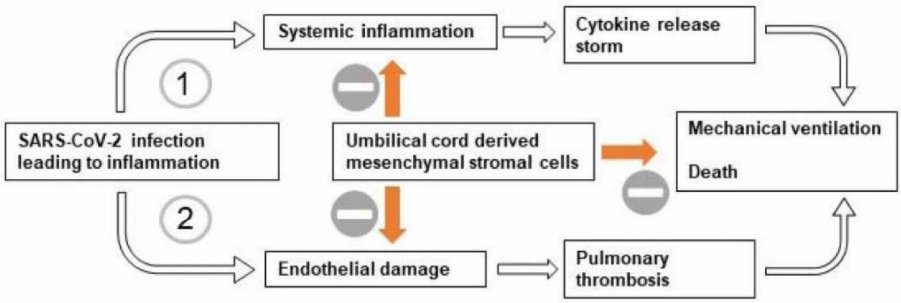


Figure 1. Unique qualities of UC-MSC that might save COVID-19 patients

UC-MSC have unique qualities, which makes them a very attractive cell compound in COVID-19 patients. They exhibit a potent **anti-inflammatory activity reducing CRS in conditions like graft versus host disease,** and the potential to ameliorate SARS-CoV2 induced lung injury by **improving the integrity of already damaged endothelium**[3] (see figure 1). UC-MSC have several other advantages; (a) they represent fetal tissue, (b) are readily available in large quantities and are GMP approved, and (c) do not require invasive techniques, in contrary to e.g. bone-marrow derived (BM-)MSC. Furthermore, they are more immune-evasive with regard to their ability to interfere with the function of antigen-presenting cells and are less rigid compared to BM-MSC, reducing possible risk of pulmonary embolism upon administration in critical COVID-19 patients[4]. Therefore we think that UC-MSC are a very promising cell therapy and **could potentially reduce mortality and need for mechanical ventilation**. We propose to perform a phase-I and subsequent phase-II study with UC-MSC in critical COVID-19 patients with respiratory insufficiency.

The **key objectives of this project** are:

1. Assess the safety of UC-MSC in critical COVID-19 patients with respiratory failure;
2. Evaluate the feasibility and potential of UC-MSC in critical COVID-19 patients;
3. Investigate the effect of UC-MSC on immuno-metabolic profiles to find new prognostic biomarkers for disease progression and UC-MSC response (patient selection), and understanding underlying mechanisms of UC-MSC mode of action.

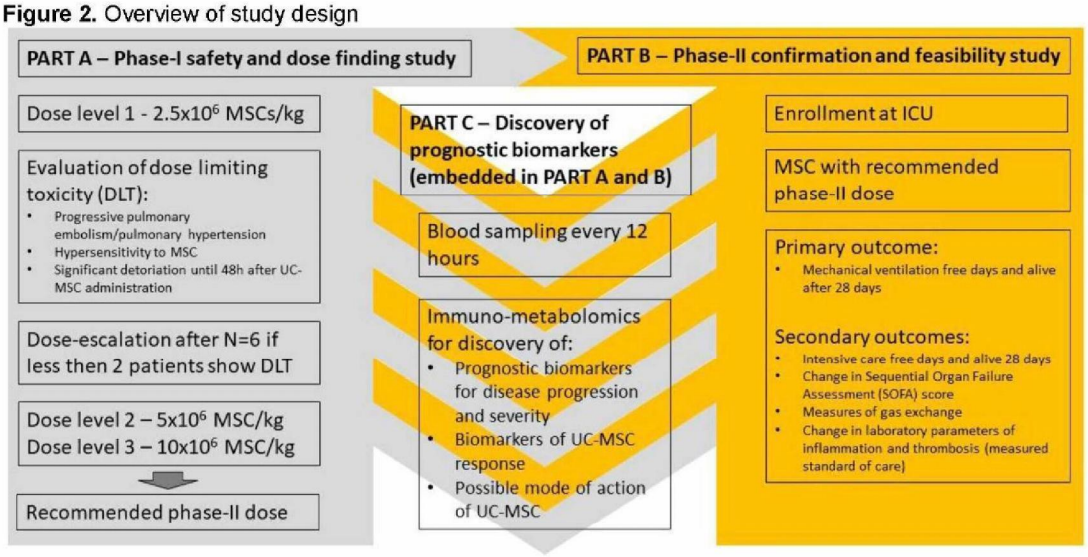
2. PLAN VAN AANPAK:

STUDY DESIGN: We will perform 2 consecutive studies with 3 main outcome parts (A-C); **a phase-I safety and dose finding study (part A) and phase-II confirmation and feasibility study (part B)**. In both studies we will collect blood samples to study disease and therapeutic mechanics by investigating immunometabolism (**part C**). These results will enable us to better predict and identify patients which will benefit from this new treatment and can be included in a larger phase III-trial, which is critical as next step. An overview of the study design is depicted in **figure 2.**

Targeted study population: Adults will be recruited at the level III ICU of the Erasmus Medical Center in Rotterdam, the Netherlands.

Inclusion criteria: Positive testing for SARS-CoV-2; Invasive mechanical ventilation <72 hours; age ≥ 18 years; signs of systemic inflammation (H-score >104 (Mehta et al. [5]; composite score for secondary haemophagocytic lymphohystiocytosis); written informed consent from patient or legal representative.
Exclusion criteria: Patient currently on ECMO; invasive mechanical ventilation for ≥ 72 hours; patients who are pregnant or who give breastfeeding; patients with active malignant tumours; uncontrolled co-infections with other viruses or bacteria; aspergillum pneumonia.

Figure 2. Overview of study design



Part A – Phase-I safety and dose finding study
The dose levels (between 5 and 20x10^6 UC-MSC per kg) are based on clinical phase I/II ARDS-trials using BM-MSCs [6], and pathophysiological repeated dosing seems sensible due to the complex responses in the first days of the disease. Six patients will receive dose level 1 (2 doses of 2.5x10^6 UC-MSC/kg with 48 hour interval) and if ≤1 patient shows a **dose limiting toxicity (DLT, see figure 2)**, we will proceed to dose level 2 (5x10^6 UC-MSC twice). Dose level 3 is the final step (10x10^6 MSC twice), unless two or more DLT occur, which prompts a de-escalation to a lower dose level. Depending on the effect and observed DLTs, the **recommended phase II dose (RP2D)** will be defined. Recruitment is stopped after each patient until possible acute DLT have been diagnosed or ruled-out (up to 48h after last administration of UC-MSC).

Part B – Phase-II confirmation and feasibility study
Effectiveness of the UC-MSC will be assessed in a feasibility study in critical COVID-19 patients, who will receive RP2D established in part A. The primary outcome is mechanical ventilation free days and alive at 28 days. We chose this primary end-point since duration of mechanical ventilation is the most important reason for ICU admittance. Reducing mortality and mechanical ventilation days decreases the burden of COVID-19 on ICU capacity. Secondary outcomes include: intensive care free days and alive after 28 days; change in Sequential Organ Failure Assessment (SOFA) score, measures of gas exchange and laboratory parameters of inflammation and thrombosis (measured standard of care).

We would consider a **reduction in mechanical ventilation of 4 days a success** (reduction of ~20%), which makes UC-MSC-therapy worth further evaluation in a phase-III study. To evaluate these rates with a significance level α=0.05, power=80% 26 patients are needed. Including the 6 patients from part A with the same dose, we need an additional 20 patients in this feasibility trial. We will compare study patients with non-included patients and the available historical cohort of COVID-19 patients admitted to the ICU.

Part C – Discovery of prognostic biomarkers for disease progression and UC-MSC response
We will acquire 0.3 ml plasma before start of, and during UC-MSC therapy (every 12 hours). In these blood samples, we aim to longitudinally measure ~200 immuno-metabolites hypothesized to be involved in the immune modulating effect of UC-MSC, including bioactive lipids playing a key role in inflammation, oxidative stress, vascular dysfunction and immune dysfunction (measured by Leiden University). By investigating these metabolites and their change overtime we aim to investigate: **a) new prognostic biomarkers** for disease progression and severity (patient selection); b) prognostic biomarkers for clinical response to UC-MSC administration (patient selection and timing of repeat dose); c) the possible mode of action of UC-MSC (underlying mechanisms). These findings may support development of new prognostic biomarkers and possible therapeutic targets.

3. HAALBAARHEID VAN HET PROJECT:

MOTIVATION FEASIBILITY: The design of this study is highly feasible. The UC-MSC product is already available. The ICU of the Erasmus Medical Center provides 60 beds for critical patients with COVID-19. Based on conservative assumptions we expect that 100 patients are eligible per year. We estimate that ~40% of these patients will be excluded based on the exclusion criteria. Assuming that about three quarter of the patients will provide informed consent, we expect that ~10 patients can be included per quarter. The ICU of the Erasmus Medical Center is well equipped and has experience in performing intervention studies. Furthermore, the applicants and their team have a long-standing history in ventilation research.
TIME SCHEDULE AND EXPECTED MILESTONES: We already are preparing the study: medical ethical approval will be submitted May 2020 and the study drug is available. We expect that duration of the part A will be 6 months (Milestone 1: open-access publication of phase-I trial, early 2021) and for part B another 6 months. Together with data cleaning and analysis, we expect a total project duration of 24 months, starting as soon as the financial support is available from July 30th 2020 (phase-I-trial preparation; 1 month initiation time (informing staff, nurses and developing lay patient folders)) and ending July 30th 2022 (open access publication of phase-II trial (Milestone 2)). Analysis on prognostic biomarkers of clinical course and UC-MSC response will be started after ending part A and B, scheduled at 15 months after start of this project. Reports will follow in the year thereafter (2021-2022, Milestone 3).

4. RELEVANTIE VOOR DE PRAKTIJK:

Due to the high risk of COVID-19 respiratory insufficiency, there is an overall consensus to find an effective intervention as quick as possible. Results forthcoming from this project will provide health care professionals with important information on a potential new cell therapy for critical COVID-19 patients, in whom mortality is significant. Improving mortality and reducing health care need will alleviate the ICU-capacity and enable more non-COVID regular health to be conducted.

This project will also provide crucial information for the next step; a phase-III randomized controlled trial, and also introduces MSC-therapy on the ICU. We are already in contact with colleagues in Dresden, Germany (prof. dr. Mario Rüdiger, project advisor), to collaborate on a phase-III trial internationally. A major advantage of UC-MSC, if shown effective, is that umbilical cords are available world-wide enabling easy increase of production of UC-MSC and implementation of this innovative cell therapy.

Also, results and knowledge forthcoming from this project can help boost MSC-therapy non-COVID-19 ARDS patients in the ICU. Furthermore, also neonates may benefit. In the department of neonatology, neonatal sepsis is a major problem with high mortality, in which UC-MSC treatment can be successful. Co-applicants (Reiss, Taal, Simons) from our study group are performing pre-clinical studies with UC-MSC and neonatal sepsis, and are keen to take UC-MSC forward in a phase-I/II trial in neonatal sepsis, for which knowledge from this project can contribute.

5. DEELNAME VAN DE STAKEHOLDER(S) (e.g. patiënten, zorgprofessionals, etc.):

As 5.1.2e 5.1.2e (main applicant) is well known and respected, ensuring effective spread of a potential novel therapy on all ICUs in the Netherlands, if shown effective. By collaborating with prof. dr. Mario Rüdiger (project advisor), from the Technical University of Dresden, Germany, we aim to contribute to a subsequent international phase-III randomized controlled trial. At this non-profit organisation, the UC-MSC are GMP manufactured (see appendix; GMP certificate) and readily available, ensuring availability of the study drug. We will also collaborate with prof. dr. 5.1.2e 5.1.2e (project advisor), head of the Leiden Academic Center of Drug Research. He has experience in performing large-scale metabolomics studies. His experience in combining clinical and basic research ensures effective study of prognostic biomarkers for clinical course and UC-MSC response.

Due to the time limitations there was no yet a response asked from patient organizations. However it is planned to ask FCIC (Family and patient Centred Intensive Care) and ICConnect, two platforms for ICU patients and their relatives.

6. LITERATUURREFERENTIES (optioneel):

1. Guan, W.J., et al. N Engl J Med, 2020. p 1708-1720
2. Oudkerk, M., et al. Radiology, 2020: p. 201629.
3. Krampera, M., et al. Blood, 2003. **101**(9): p. 3722-9.
4. Castro-Manrreza, M.E., et al. Stem Cells Dev, 2014. **23**(11): p. 1217-32.
5. Mehta, P., et al. Lancet, 2020. **395**(10229): p. 1033-1034.
6. Matthay, M.A., et al. Lancet Respir Med, 2019. **7**(2): p. 154-162

LANDESDIREKTION SACHSEN | Freistaat SACHSEN

Zertifikat-Nr./Certificate no:
DE_SN_01_GMP_2017_0007

Aktenzeichen/Reference Number:
L24-5115/277

BESTÄTIGUNG DER ÜBEREINSTIMMUNG EINES HERSTELLERS MIT GMP

Teil 1

Ausgestellt nach einer Inspektion gemäß

- **Art. 111 (5) der Richtlinie 2001/83/EG**
- **Art. 15 der Richtlinie 2001/20/EG**

Die zuständige deutsche Überwachungsbehörde bestätigt:

Der Hersteller
Universitätsklinikum Carl Gustav Carus Dresden an der Technischen Universität Dresden (AöR)

Anschrift der Betriebsstätte
Medizinische Klinik und Poliklinik I
Fetscherstraße 74
Haus 27, Haus 31, Haus 59, Haus 65, Haus 66, Haus 85, Haus 111
01307 Dresden
Deutschland

- wurde im Rahmen der nationalen Arzneimittelüberwachung inspiziert in Verbindung mit der Herstellungserlaubnis Nr. DE_SN_01_MIA_2016_0047 gemäß
  - Art. 40 der Richtlinie 2001/83/EG
  - Art. 13 der Richtlinie 2001/20/EG

umgesetzt in deutsches Recht durch:
§ 13 Abs. 1 und § 72 Arzneimittelgesetz

Aufgrund der aus der letzten Inspektion vom 25. November 2016 gewonnenen Erkenntnisse wird für die oben genannte Betriebsstätte des Herstellers die Übereinstimmung mit den Anforderungen der Guten Herstellungspraxis festgestellt, die sich aus

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER

Part 1

Issued following an inspection in accordance with

- **Art. 111 (5) of Directive 2001/83/EC**
- **Art. 15 of Directive 2001/20/EC**

The competent authority of GERMANY confirms the following:

The manufacturer
Universitätsklinikum Carl Gustav Carus Dresden an der Technischen Universität Dresden (AöR)

Site address
Medizinische Klinik und Poliklinik I
Fetscherstraße 74
Haus 27, Haus 31, Haus 59, Haus 65, Haus 66, Haus 85, Haus 111
01307 Dresden
Germany

- has been inspected under the national inspection programme in connection with manufacturing authorisation no. DE_SN_01_MIA_2016_0047 in accordance with
  - Art. 40 of Directive 2001/83/EC
  - Art. 13 of Directive 2001/20/EC

transposed in the following national legislation:
Sect 13 para 1 and sect 72 Arzneimittelgesetz (German Drug Law)

From the knowledge gained during the inspection of this manufacturer, the latest of which was conducted on 25 November 2016, it is considered that it complies with the Good Manufacturing Practice requirements referred to in

5.1.2e

Unterschrift: 5.1.2e

LANDESDIREKTION SACHSEN

• den Grundsätzen und Leitlinien der Guten Herstellungspraxis gemäß
  - Richtlinie 2003/94/EG

ergeben.

Dieses Zertifikat bestätigt den Status der Betriebsstätte zum Zeitpunkt der oben genannten Inspektion. Es sollte nicht zur Bestätigung der Übereinstimmung herangezogen werden, wenn seit der genannten Inspektion mehr als drei Jahre vergangen sind. Nach Ablauf dieser Zeit sollte mit der zuständigen Behörde Kontakt aufgenommen werden. Das Zertifikat ist nur bei Vorlage sämtlicher Seiten inklusive der Teile 1 und 2 gültig. Die Echtheit dieses Zertifikates kann ggf. durch die ausstellende Behörde bestätigt werden.

• the principles and guidelines of Good Manufacturing Practice laid down in
  - Directive 2003/94/EC

This certificate reflects the status of the manufacturing site at the time of the inspection noted above and should not be relied upon to reflect the compliance status if more than three years have elapsed since the date of that inspection, after which time the issuing authority should be consulted. This certificate is valid only when presented with all pages and both parts 1 and 2. The authenticity of this certificate may be verified with the issuing authority.

FREISTAAT SACHSEN
LANDESDIREKTION SACHSEN

5.1.2e

Unterschrift: 5.1.2e

Teil 2	Part 2
• Humanarzneimittel • Prüfpräparate zur Anwendung am Menschen der Phasen I, II, III	• Human Medicinal Products • Human Investigational Medicinal Products for phase I,II,III
1 HERSTELLUNGSTÄTIGKEITEN	**1 MANUFACTURING OPERATIONS**
- Die erlaubten Herstellungstätigkeiten umfassen vollständige und teilweise Herstellung (einschließlich verschiedener Prozesse wie Umfüllen, Abpacken oder Kennzeichnen), Chargenfreigabe und -zertifizierung, Lagerung und Vertrieb der genannten Darreichungsformen sofern nicht anders angegeben;	- authorised manufacturing operations include total and partial manufacturing (including various processes of dividing up, packaging or presentation), batch release and certification, storage and distribution of specified dosage forms unless informed to the contrary;
- Die Qualitätskontrolle und/oder Freigabe und/oder Chargenzertifizierung ohne Herstellungsschritte sollten unter den entsprechenden Punkten spezifiziert werden;	**- quality control testing and/or release and batch certification activities without manufacturing operations should be specified under the relevant items;**
- Unter der relevanten Produktart und Darreichungsform sollte auch angegeben werden, wenn der Hersteller Produkte mit speziellen Anforderungen herstellt, z.B. radioaktive Arzneimittel oder Arzneimittel, die Penicilline, Sulfonamide, Zytostatika, Cephalosporine, Stoffe mit hormoneller Wirkung oder andere potenziell gefährliche Wirkstoffe enthalten (anwendbar für alle Bereiche des Teils 1 mit Ausnahme 1.5.2 und 1.6).	- if the company is engaged in manufacture of products with special requirements e.g. radiopharmaceuticals or products containing penicillin, sulphonamides, cytotoxics, cephalosporins, substances with hormonal activity or other or potentially hazardous active ingredients this should be stated under the relevant product type and dosage form (applicable to all sections of Part 1 apart from sections 1.5.2 and 1.6)
1.3 Biologische Arzneimittel	**1.3 Biological medicinal products**
1.3.1 Biologische Arzneimittel	*1.3.1 Biological medicinal products*
1.3.1.5 Biotechnologische Produkte	1.3.1.5 Biotechnology products
1.6 Qualitätskontrolle	**1.6 Quality control testing**
1.6.4 Biologisch	*1.6.4 Biological*

22. Februar 2017

FREISTAAT SACHSEN
LANDESDIREKTION SACHSEN

22 February 2017

Name und Unterschrift des Bearbeiters der zuständigen Behörde

5.1.2e

5.1.2e

5.1.2e

Referat 24, Pharmazie, GMP-Inspektorat
Braustraße 2
04107 Leipzig
Deutschland

Tel.: + 5.1.2e

Name and signature of the authorised person of the Competent Authority

5.1.2e

5.1.2e

5.1.2e

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