

Setting Up A Serum Eye Drops Program

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This presentation shares our experience on how to use the synergies of being a blood and tissue bank when starting a serum eye drops (SED) program

Though the process might not be familiar to eye bankers, it is strongly related to eye banks and their end users



BLUTZENTRALE LINZ

2018:
 > 50.000 blood donations
 > 500 tissue donations
 (allogeneic + autologous)

BLOOD PRODUCTS + MEDICINAL PRODUCTS



clean rooms (GMP class D)
for separation of blood components





Plasma
Erythrocytes
Thrombocytes
Serum eye drops
+
medicinal products for clinical studies



CELL AND TISSUE PRODUCTS



Cornea, DMEK, sclera



Heart valve and aorta



Amnion

clean rooms for cell and tissue banking
(GMP class D, C, B, A)





Cranial bone



Ovarian tissue



stem cell apheresis

OTHER AREAS:

- Blood donation
- Outpatient clinics
- Hematology and Immunhematology
- PCR- and ELISA-screening of products
- Microbiology, Immunogenetics
- R&D: Tissue Regeneration with LBI Trauma

Red Cross Blood Transfusion Service of Upper Austria runs a blood and tissue bank with more than 50.000 blood and 500 tissue donations, mainly serving the federal state of Upper Austria.

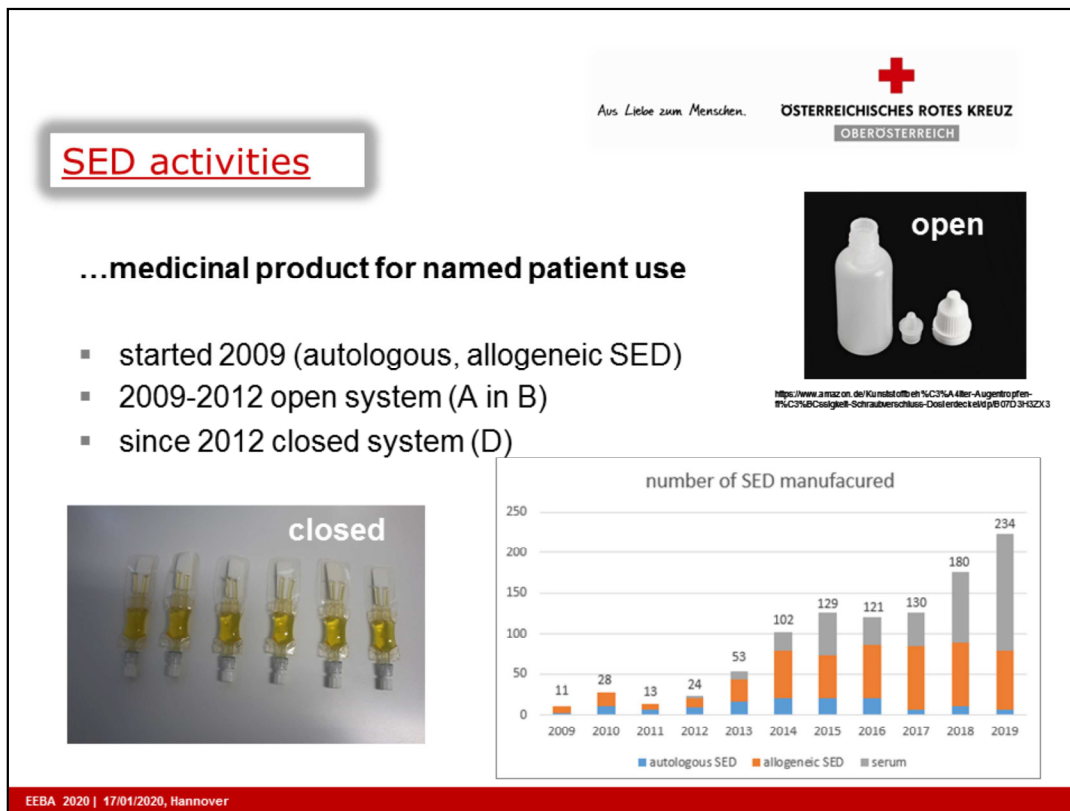
- Three different blood products (erythrocytes, thrombocytes, plasma)
- Two classical medicinal products (one investigational medicinal product and serum eye drops)
- Eight different autologous and allogeneic tissues and cells (cornea, DMEK, sclera, heart valves, amniotic membrane, cranial bone, ovarian tissue, peripheral blood stem cells)

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- Our serum eye drops program started on request of some of our cooperating ophthalmologists of our eye bank in 2009.
- SED are classified as classical medicinal products in AT.
- Named patient use only way to overcome required registration of medicinal product
- Until 2012 both autologous and allogeneic SED processed with open system (filling performed in laminar air flow class A with B-background)
- Since 2012 closed SED processing system from company „Meise Medizintechnik“ in use → transfer of processing to clean room class D
- Steadily growing number of serum units and patients within the last decade (in 2019 processing of 234 serum donations)

SYNERGIES	BLOOD BANK REQUIREMENTS	TISSUE BANK REQUIREMENTS	ADDITIONAL REQUIREMENTS
Blood donor evaluation	X	-	-
Blood donor procurement	X	-	-
Blood donor testing	X	-	-
QMS	X	X	-
Premises	X	X	-
Processing in clean room	X (grade D)	X (grade D, C, B)	-
Storage	X (-30°C up to room temperature)	X (LN-tanks up to 31°C)	-
ISBT128 coding	X	X	-
QC	X (infectious diseases, sterility, cell counting)	X (infectious diseases, sterility, cell counting)	Stability program
Distribution	X	X	Via pharmacy
Traceability	X	X	-
Vigilance	X	X	-
Clinical application	-	Ophthalmologists	Prescription (named-patient use)
Release	X	X	Head of Production Head of Quality Control Qualified Person
Retention samples	X	X	also for consumables and reagents

When implementing SED program, synergies of being a blood and tissue bank could be perfectly used.

What could blood and tissue activities offer to fulfill medicinal product requirements?

- 1) Blood donation and testing is already in place.
- 2) Benefit from already existing quality management system, premises as well as knowledge about processing storage, coding distribution traceability vigilance, quality control and release

What needs to be established additionally?

- 1) Set up of stability program for SED
- 2) Distribution of SED via pharmacy
- 3) Named-patient use prescription by ophthalmologist
- 4) Three legal functions need to be implemented (Head of Production, Head of Quality Control, Qualified Person)

Blood donation

- **Meise TF304** Blood collection system for serum eye drops:
Triple bags 1 x 500 ml, 2 x 300 ml
- **450ml blood donation**



OSTERREICHISCHES ROTES KREUZ

VOM MEDIZINISCHEN PERSONAL AUSZUFÜLLEN

GESUNDHEITSFRAGENBOGEN

Als Blutspender können Sie zu jedem Zeitpunkt des Spendenlaufes proben, ohne Angabe von Gründen und ohne Unannehmlichkeiten von Ihrer Blutspende zurücktreten (freiwilliger Selbstauschluss).

Bin ich bereit?

Familienname: _____ Geb. Datum: _____ Frau: ☐ Größe: _____

Vorname: _____ Tel. Nr.: _____

Strasse: _____ E-Mail: _____

PLZ/Ort: _____ Bitte Zutreffendes ankreuzen:

1. Fühlen Sie sich gesund?



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If all requirements for whole blood donation, as given in blood directives, are fulfilled, 450 mL whole blood with TF304 system without any anticoagulant can be withdrawn.

SED processing

- **Clotting** (min. 2 hours at room temp.)
- **Centrifugation 2x**
- **Separation 2x**
- **Meise TF36** Eye drop system
36 application receptacles, 1 transfer bag 300 ml
→ **SED receptacles** (for direct patient use)
→ **or serum bags** (delivered as raw material)
- **Labelling, packaging**
- **Freezing at -30°C**

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Blood clotting is awaited for at least two hours at room temperature. Blood bag is centrifuged and separated twice.


Then, obtained serum is either aliquoted to SED receptacles in closed TF36 system or kept in transfer bag and stored as serum raw material for another blood bank, which processes diluted SED.

Quality control

- HIV, HCV, TPHA, HSV, CMV tested
- Residual blood count
- Free hemoglobin
- **Sterility (blood culture testing), aerob, anaerob**
- **Stability program**

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- QC performed contemporaneously for each product (infect marker, residual blood count, free hemoglobin and sterility)
- Additionally a yearly stability program is mandatory.



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Quality control – sterility testing

- until 2019 direct inoculation (Ph.Eur. 2.6.1)
- now: BactAlert BPA + BPN (Ph.Eur.2.6.27)

Validation results

....problems with detection of Bacteroides fragilis

- Influence of product age on detection
→ **same-day testing**
- Delayed detection
→ **prolonged incubation**
from 7(dir. inoc.) to 14 days (blood cult.)

Erreger	Produktart	AK1	AK2	AK3	AK4	AK5
Aspergillus brasiliensis	SAT Patienten	erfüllt	erfüllt	erfüllt	erfüllt	erfüllt
	SAT England	erfüllt	erfüllt	erfüllt	erfüllt	erfüllt
Bacillus subtilis	SAT Patienten	erfüllt	erfüllt	erfüllt	erfüllt	erfüllt
	SAT England	erfüllt	erfüllt	erfüllt	erfüllt	erfüllt
Candida albicans	SAT Patienten	erfüllt	erfüllt	erfüllt	erfüllt	erfüllt
	SAT England	erfüllt	erfüllt	erfüllt	erfüllt	erfüllt
Pseudomonas aeruginosa	SAT Patienten	erfüllt	erfüllt	erfüllt	erfüllt	erfüllt
	SAT England	erfüllt	erfüllt	erfüllt	erfüllt	erfüllt
Staphylococcus aureus	SAT Patienten	erfüllt	erfüllt	erfüllt	erfüllt	erfüllt
	SAT England	erfüllt	erfüllt	erfüllt	erfüllt	erfüllt
Bacteroides fragilis	SAT Patienten	erfüllt	erfüllt	nicht erfüllt - Abweichung	erfüllt	erfüllt
	SAT England	erfüllt	erfüllt	erfüllt	erfüllt	erfüllt
Clostridium sporogenes	SAT Patienten	erfüllt	erfüllt	erfüllt	erfüllt	erfüllt
	SAT England	erfüllt	erfüllt	erfüllt	erfüllt	erfüllt
Culibacterium acnes	SAT Patienten	erfüllt	erfüllt	erfüllt	erfüllt	erfüllt
	SAT England	erfüllt	erfüllt	erfüllt	erfüllt	erfüllt

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- Up to end of 2019 obliged to perform direct inoculation for SED sterility testing (according to Ph.Eur. 2.6.1) within a LAF class A with background B
- Requirements changed → back with sterility testing with blood culture testing (BactAlert System) with inoculation in a LAF class A with background D
- During method validation one deviation found → problems with detection of bacterioides fragilis
 - a) product age has impact (testing needs to be started on day of production)
 - b) delay in detection (incubation time to be prolonged)

Stability program

- In 2014: proteomics analysis (2D-gel electrophoresis)

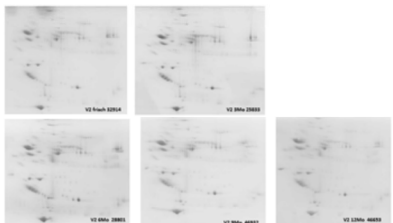


Abbildung 5: Versuch V2 (3005404)

Protein count (quantitative)	Fresh	3 months	6 months	9 months	12 months
Mean	131	123	124	108	91

Curr. Eye Res. 2011 Sep;36(9):775-81. doi: 10.3109/02713683.2011.587935.
Stability of epitheliotrophic factors in autologous serum eye drops from chronic Stevens-Johnson syndrome dry eye compared to non-autoimmune dry eye.
Phasukkijwatana N¹, Lertit P, Liammongkolkul S, Prabhasawat P.

Br J Ophthalmol. 1999 Apr;83(4):390-5.
Treatment of dry eye by autologous serum application in Sjögren's syndrome.
Tsubota K¹, Goto E, Fujita H, Ono M, Inoue H, Saito J, Shimmura S.

Br J Ophthalmol. 2004 Nov;88(11):1467-74.
Autologous serum eye drops for ocular surface disorders.
Geerling G¹, MacLennan S, Hartwig D.

Cornea. 2012 Nov;31(11):1313-8. doi: 10.1097/ICO.0b013e3182542085.
Stability of serum eye drops after storage of 6 months.
Fischer KR¹, Qipitz A, Böeck M, Geerling G.

Stability testing as additional requirement for medicinal products

First step was to assess shelf life:

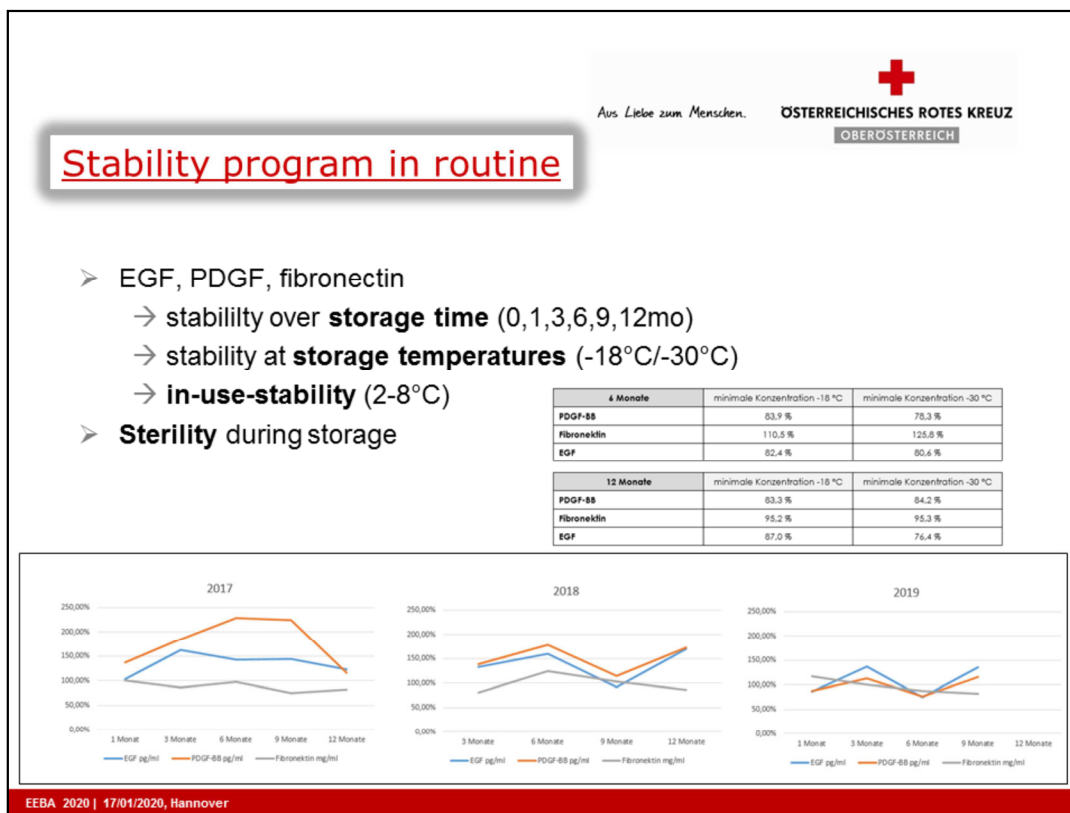
- several surrogate proteins chosen on the basis of literature research → EGF (endothelial growth factor), PDGF (platelet derived growth factor), fibronectin → proteomic analysis with 2D-gel electrophoresis → stable protein count for up to 6 months accompanied by negative sterility testing

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Since 2017 our SED stability program is performed routinely. Surrogate proteins are tested for storage time and temperature in order to constantly monitor quality of SED.


- Surrogate proteins stable for up to 6 months/ no difference between -30°C storage at blood bank and -18°C in domestic freezer/ all SED remained sterile
- In-use stability testing to be established to verify that quality can be retained in one receptacle for one day, once container is opened by patient
- In-use stability testing performed after 3 months → after first use of container a drop was squeezed out every two hours (in-between storage at 2-8°C) → surrogate proteins and sterility tested and comparable to stability data at same time point



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Release of SED

- release by **Head of Production/ Head of Quality Control/ Qualified Person**
- distribution via **pharmacy**
- delivered with logistics (**dry ice**)
- **Domestic freezer (-18°C)**



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Some additional requirements need to be fulfilled also when distributing SED

- SED need to be officially released by Head of Production, Head of Quality Control and Qualified Person
- Only then SED can be distributed, but formally only by a pharmacy.