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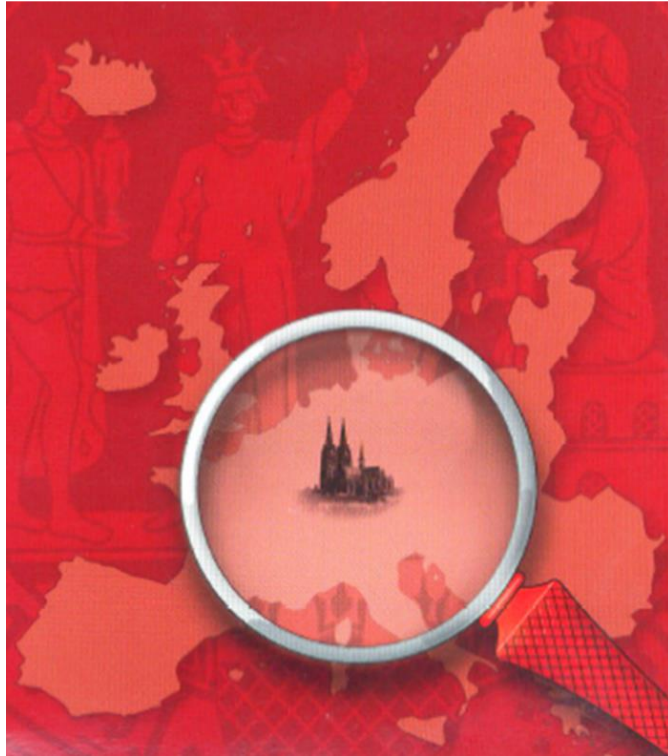
**Transfusionsmedizin  
Blutspendezentrale**

An example of preparation process authorization:  
serum eye drops

Prof. Birgit Gathof



# Cologne approach and results



- Introduction
- Development of manufacturing process
- Retrospective clinical evaluation of patients
- Evaluation of technical problems during manufacturing, storage delivery or application
- Technical and logistic suggestions



# Background

- *First use of serum eye drops described by Fox, 1984*
- *Description of use: Tsubota et al. 1999*
- *Comparison of preparation fo eye drops from serum / plasma (centrifugation, content of postulated active substance), Geerling 2004*



# ? active substance ?

- VEGF-A ? Sanak F. et al, 2022



# Overview on first clinical studies

## (Geerling et al 2004)

Production conditions and results of studies published. Success is defined either as number of all eyes/patients improving or as reduction of mean baseline (as stated in the paper) of fluorescein, rose bengal positive epitheliopathy (objective), or symptoms (subjective) score

| Author                     | Year | Concentration/diluent        | Centrifugation (g force/duration) | Clotting time | Frequency/remarks | Indication  | Eyes (patients) | Success objective        | Success subjective |
|----------------------------|------|------------------------------|-----------------------------------|---------------|-------------------|-------------|-----------------|--------------------------|--------------------|
| Fox <sup>1</sup>           | 1984 | 33%/0.9% NaCl                | 500 g/10 min                      | NR            | 2 hourly          | KCS         | 30 (15)         | RB 41%                   | 51%; 15 (15)       |
| Tsubota <sup>2</sup>       | 1999 | 20%/NaCl                     | 1500 rpm/5 min                    | NR            | 6–10×             | KCS in SS   | 24 (12)         | Fl: 55 %; RB: 68%        | 34 %               |
| Rocha <sup>35</sup>        | 2000 | 33%/0.9% NaCl                | 500 g/10 min                      | NR            | Hourly, filtered  | KCS in GVHD | 4 (2)           | 4 (4)                    | 4 (4)              |
| Poon <sup>33</sup>         | 2001 | 50–100%/0.5% chloramphenicol | 4000 rpm (2200 g)/10 min          | 2 h           | 8×                | KCS         | 11 (9)          | Fl: 6 (11) BR: 5 (11)    | 6 (11)             |
| Tananuvat <sup>38</sup>    | 2001 | 20%/0.9% NaCl                | 4200 rpm/15 min                   | NR            | 6×                | KCS         | 12 (12)         | Fl: 39%; RB: 33% IPC 44% | 36% (NS)           |
| Takamura <sup>37</sup>     | 2002 | 20%/0.9% NaCl                | 3000 rpm/10 min                   | NR            | 4–8×              | KCS         | NR (26)         | “improved”               | 20 (26)            |
| Ogawa <sup>36</sup>        | 2003 | 20%/0.9% NaCl                | 1500 rpm/5 min                    | NR            | 10×               | KCS in GVHD | 28 (14)         | Fl: 61%, RB 40%          | 30 %               |
| McDonnell <sup>47</sup>    | 1988 | 100%                         | NC/15–20 min                      | 15 min        | 1–2 hourly        | PED         | 1 (1)           | IC deposition            | No                 |
| Tsubota <sup>25</sup>      | 1999 | 20%/NaCl                     | 1500 rpm/5 min                    | NR            | 6–10×             | PED         | 16 (15)         | 10 (16)                  | NR                 |
| Poon <sup>33</sup>         | 2001 | 50–100%/0.5% chloramphenicol | 4000 rpm (2200 g)/10 min          | 2 h           | 8×                | PED         | 15 (13)         | 9 (15)                   | NR                 |
| De Souza <sup>42</sup>     | 2001 | 100%                         | NC                                | NR            | Hourly            | PED/PK      | 70 (63)         | 57 (70)                  | NR                 |
| Garcia <sup>43</sup>       | 2003 | 20%/0.9% NaCl                | 5000 rpm/10 min                   | NR            | 10×               | PED         | 11 (11)         | 6 (11)                   | NR                 |
| Tsubota <sup>45</sup>      | 1996 | 20%/NaCl                     | 1500 rpm/5 min                    | NR            | ¼ hourly          | LSC-Tx, PK  | 14 (11)         | 12 (14)                  | NR                 |
| Poon <sup>33</sup>         | 2001 | 50–100%/0.5% chloramphenicol | 4000 rpm (2200 g)/10 min          | 2 h           | 8×                | PK          | 2 (2)           | 2 (2)                    | NR                 |
| Del Castillo <sup>41</sup> | 2002 | 20%/0.9% NaCl                | 1500 rpm/5 min                    | NR            | 3×                | RES         | 11 (11)         | 8 (11); RoR: 99%         | NR                 |
| Goto <sup>40</sup>         | 2001 | 20%/0.9% NaCl                | 1500 rpm/5 min                    | NR            | 10×               | SLK         | 22 (11)         | Fl 88%, BR 91% IPC 100%  | 21%, 9 (11)        |
| Noble <sup>39</sup>        | 2003 | 50%/0.9% NaCl                | NR                                | 48–72 h       | Replacement       | OSD         | 32 (16)         | IPC 9 (25)               | 10 (16)            |
| Matsumoto <sup>20a</sup>   | 2004 | 20%/NaCl                     | 3000 rpm/10 min                   | NR            | 5–10×             | NK          | 14 (11)         | 14 (14)                  | NR                 |

Note that the scale used to measure these changes as well as the baseline level varied between the studies. GVHD: graft versus host disease; IC: immune complex; IPC: impression

# Controlled studies for SED

| authors                  | diagnosis                                       | result                           |
|--------------------------|---|----------------------------------|
| Noble et al. 2004        | Keratokonjunktivitis sicca                      | Superior to artificial tears     |
| Koijma et al. 2005       | Keratokonjunktivitis sicca,<br>Sjögren syndrome | Superior to conventional therapy |
| Noda-Tsuruya et al. 2006 | Post Lasik dry eye                              | Similar to eye drops             |
| Schulze et al. 2006      | Post-OP<br>Hornhautlesions<br>Diabetes mellitus | Lesion healing quicker with SED  |
| Uzurca et al. 2012       | Severe dry eye                                  | Superior to conventional therapy |
| Lopes-Garcia et al. 2014 | Sjögren syndrome                                | Superior to conventional therapy |
| Celebi et al. 2014       | Very severe dry eye                             | Superior to conventional therapy |



# Clinical indications for SED

## Diseases of the surface of the eye

- 👁️ Dry eye resistant to other treatment
- 👁️ Persisting epithelial defect
- 👁️ Neurotrophic Keratopathy
- 👁️ Ulcus corneae



# Cologne results

## Introduction

## experience of manufacturing serum eye drops

-  > 10 year's autologous

-  > 5 year's allogeneous

## Technical and logistic aspects





# Legal frame in Germany

- Serum eye drops are regarded as drug
- Manufacturing and application is possible if done by the same physician
- Delivery to patients is only permitted
  - with license for manufacturing
  - via a pharmacy only



# Time line

- Summer 2011: first plans
- Autumn/winter 2011: validation, establishment of quality management
- 27.1.2012 license to manufacture issued
- Since March 2012 manufacturing of SED in closed system





# Quality management

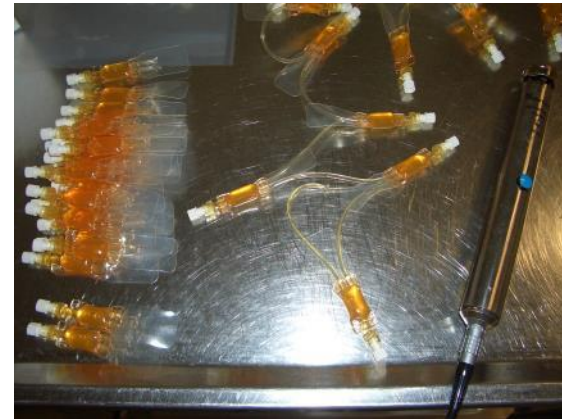
- Project plans
- SOP, documents
- Forms for clinicians, pharmacies
- Documentation, data processing
- Labeling
- Quality control



# Preparation



# Filling of vials



# Quality control, packaging



# Quality control, packaging





# New vials

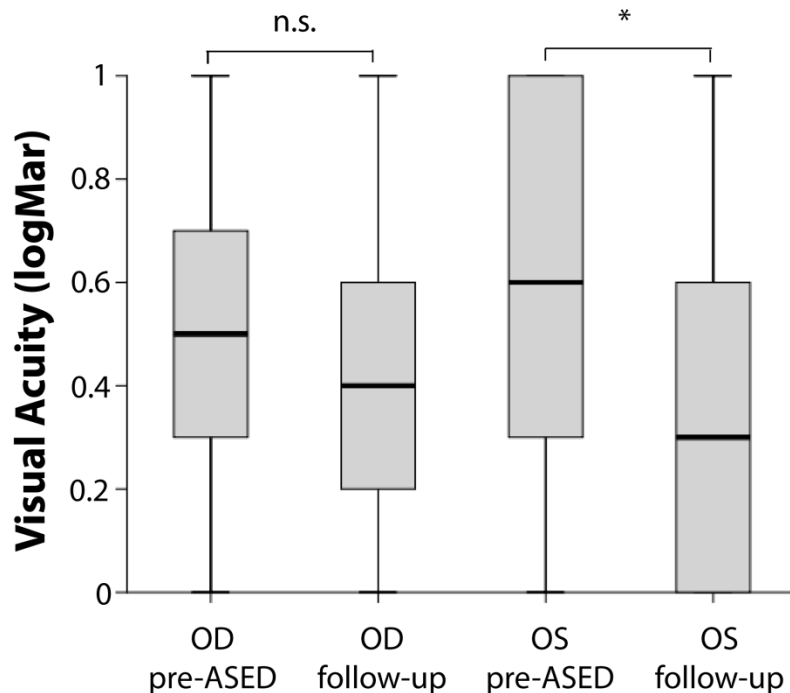


# SED Production

- Use of two different vial systems attempted to increase safety of production
- Validation of new supplier planned



# Results of 14 Pt. GvHD, before and with SED (Tahmaz et al. 2017)



The median BVCA decreased from OD  $0.5 \pm 0.32$  pre-ASED to  $0.4 \pm 0.3$  at the six month interval and OS  $0.6 \pm 0.35$  pre-ASED to  $0.3 \pm 0.35$  at the six month interval ( $P = 0.04/0.003$ )

# Time line allogeneous SED

- 2016 request for treating a child with serum eye drops
- 2017 permission of local authorities to treat patients in individual healing attempts



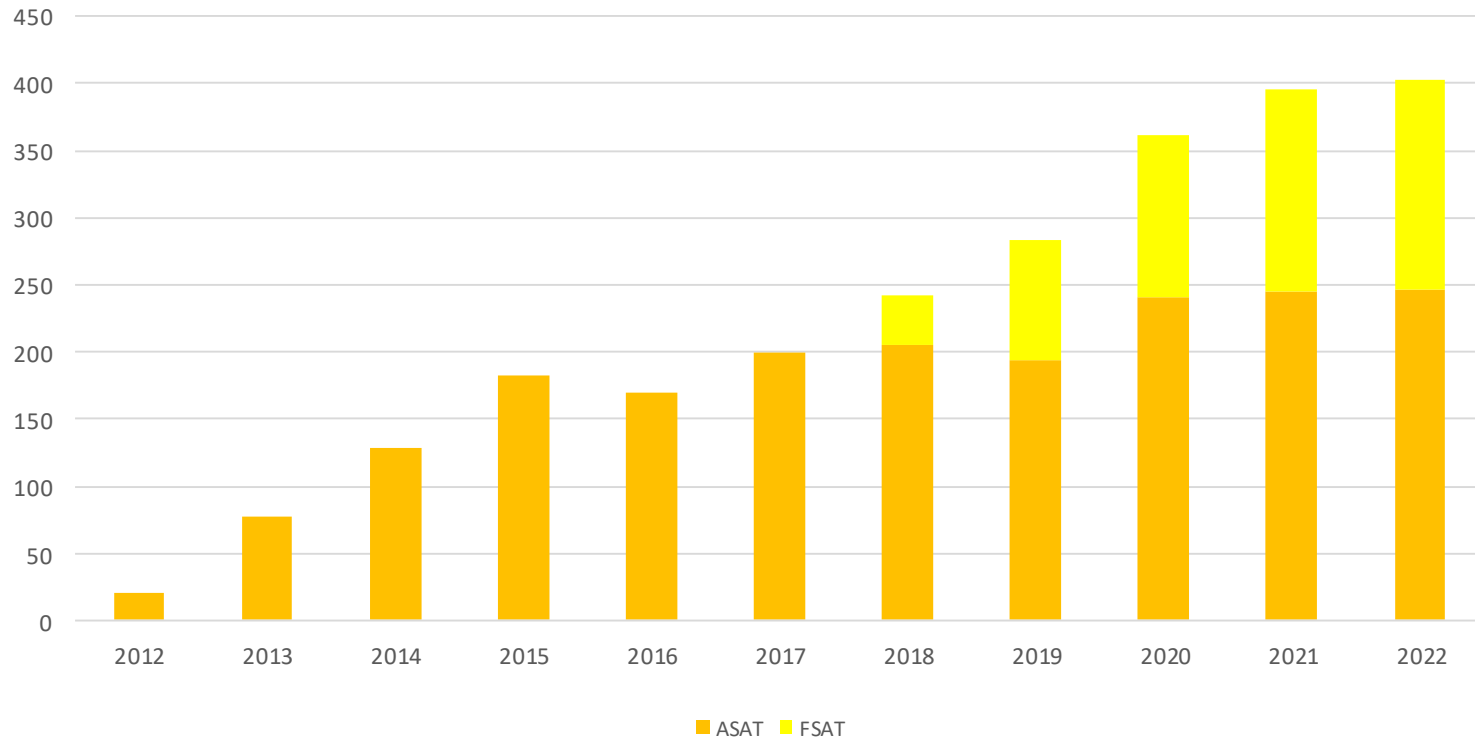
# ASED production in Cologne

- Preparation of quality management in 2017 for a child
- First manufacturing in 2017



# Production of serum eye drops 2012-2022

(ASAT = autol. SED, FSAT = allog. SED)



# ASED production in Cologne

- > 140 patients treated
  - 16 children
  - 47 previously autologous donors



# ASED: Qualification of donors

- Male repeat donor
- Informed consent
- ABO Blood group identical to patient
- Negative questionnaire for ocular disease (no dry eyes)
- Negative infectious disease history
- No high lipid meal in past 2 days





# Donor qualification for ASED

| Donor Eligibility criteria          | ABO Blood group   | Negative transfusion history | Quarantine (4 Mo.) | Male donor | Questionnaire excluding dry eyes |
|-------------------------------------|-------------------|------------------------------|--------------------|------------|----------------------------------|
| Rodriguez Calvo de Mora et al. 2021 | AB                | -                            | -                  | +          | -                                |
| Van der Meer et al. 2021            | AB                | +                            | +                  | +          | -                                |
| Gathof et al. 2020                  | Same as recipient | +                            | -                  | +          | +                                |
| Leitner et al. 2017                 | Same as recipient |                              |                    |            |                                  |









# Present problems Blood Center

- Just in time manufacturing
  - No donor available that proper day
  - Request for production higher than capacity
- Lipidemic product
- Rarely product bacterially contaminated



# Deviations






## Logistic and pharmacy

-  Dry ice not in time
-  Pharmacy not open, when transport arrived
-  Delivery to wrong adress
-  No freezer
-  Freezer broken
-  Billing problems



# Deviations

## Patients

-  Freezer broken
-  Eye drops vial not opened properly
-  Use of eye drops longer than recommended
-  Eye drops not stored as recommended
-  Eye drops smelled strange



# Cochrane Study (Pan et al. 2017)

Summary: Autologous serum eye drops may be useful, but no clear evidence more information required

- Standardization of manufacturing
- Legal aspects
- Double blinded clinical studies



# Clinical studies registered

[Home](#) > Search Results

[Modify Search](#) [Start Over](#)



19 Studies found for: **serum eye drops | Dry Eye Disease**

Also searched for **Keratoconjunctivitis Sicca, Ophthalmic Solution, Dry Eye** and more. [See Search Details](#)

[List](#) [By Topic](#) [On Map](#) [Search Details](#)

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Showing: 1-10 of 19 studies  studies per page

Filters

[Apply](#) [Clear](#)

Status

Recruitment

- Not yet recruiting
- Recruiting
- Enrolling by invitation
- Active, not recruiting
- Suspended
- Terminated
- Completed
- Withdrawn
- Unknown status†

Expanded Access

Eligibility Criteria

Age




years OR

Age Group

| Row | Saved                    | Status                 | Study Title  | Conditions          | Interventions  | Locations  |
|-----|--------------------------|------------------------|--|---------------------|--|--|
| 1   | <input type="checkbox"/> | Active, not recruiting | <a href="#">Comparison of Efficacy Between 100% Platelet-rich Plasma and 100% Serum Eye Drops in Dry Eye Disease</a> | • Dry Eye Disease   | • Drug: 100% Autologous platelet rich plasma<br>• Drug: 100% Autologous serum  | • Ophthalmology Department, Ramathibodi Hospital Ratchathewi, Bangkok, Thailand  |
| 2   | <input type="checkbox"/> | Completed              | <a href="#">Comparison of Autologous Serum and Umbilical Cord Serum Eyedrops for Dry Eye Syndrome</a>                | • Dry Eye Syndrome  | • Drug: Umbilical cord serum eyedrops<br>• Drug: Autologous serum eyedrops   | • Chonnam national university hospital Gwangju, Korea, Republic of   |
| 3   | <input type="checkbox"/> | Completed              | <a href="#">Allogeneic Versus Autologous Serum Eye Drops</a>   | • Dry Eye Syndrome  | • Other: Autologous serum eye drops<br>• Other: Allogeneic serum eye drops   | • Radboudumc Nijmegen, Netherlands   |
| 4   | <input type="checkbox"/> | Unknown †              | <a href="#">Umbilical Cord Serum Versus Conventional Eyedrops</a>  | • Dry Eye Syndromes | • Drug: Optive, Ophthalmic Solution<br>• Biological: Umbilical Cord Serum eye drops<br>• Drug: Genteal lubricant gel | • UKM Medical Centre Cheras, Kuala Lumpur, Malaysia<br>• National Blood Centre, Malaysia Kuala Lumpur, Wilayah Persekutuan, Malaysia<br>• Hospital Kuala Lumpur Kuala Lumpur, Wilayah Persekutuan, Malaysia          |
| 5   | <input type="checkbox"/> | Unknown †              | <a href="#">Assessment of the Mu-Drop System for Serum Eye Drops</a>   | • Dry Eye Syndrome  | • Other: Allogeneic conventional sized serum eye drops<br>• Other: Allogeneic micro sized serum eye drops            | • Academic Medical Center Amsterdam Amsterdam-Zuidoost, Netherlands<br>• Leiden University Medical Center Leiden, Netherlands<br>• Maastricht University Medical Center Maastricht, Netherlands<br>• (and 3 more...) |



# Perspective

-  Create more scientific evidence for therapeutic effect (national + international collaborations)
-  Optimize packaging / applicators
-  Optimize logistics



# New EU Guidelines for SoHO



Brüssel, den 14.7.2022  
COM(2022) 338 final

2022/0216 (COD)

Vorschlag für eine

**VERORDNUNG DES EUROPÄISCHEN PARLAMENTS UND DES RATES**

**über Qualitäts- und Sicherheitsstandards für zur Verwendung beim Menschen bestimmte Substanzen menschlichen Ursprungs und zur Aufhebung der Richtlinien 2002/98/EG und 2004/23/EG**

- Manufacturing according to GMP-criteria required for autologous products, when processed or stored



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Many thanks to the team:

Center for dry eyes:

Ophthalmology

Prof. Claus Cursiefen

Prof. Dr. Philip Steven

Dr. Volkan Tahmaz

Transfusionsmedizin

Aylin Pamuk

Pauline Rothbart

Dr. Viorica Petrescu

Dr. Larissa Oustianskaia

Dr. Melanie Störmer

Monika Jedrzejewska

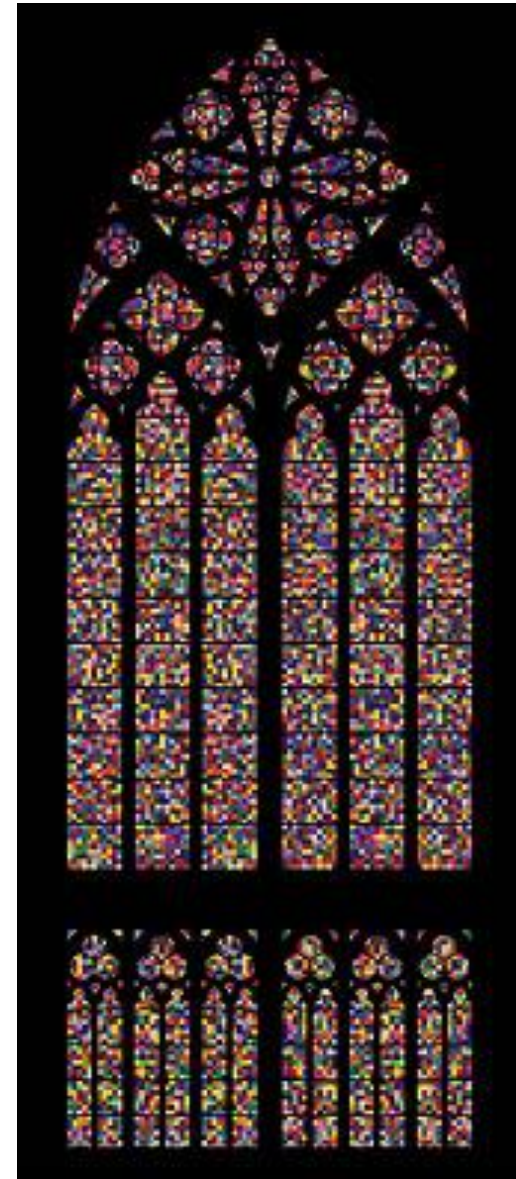
Christof Wochnik

Kerstin Flecken

Natalia Homann

Mathias Mrotzeck

Dr. Stela Radojska †



Window designed by Gerhard Richter,  
Cathedral Cologne



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