# Plasma project in Switzerland: status and next steps

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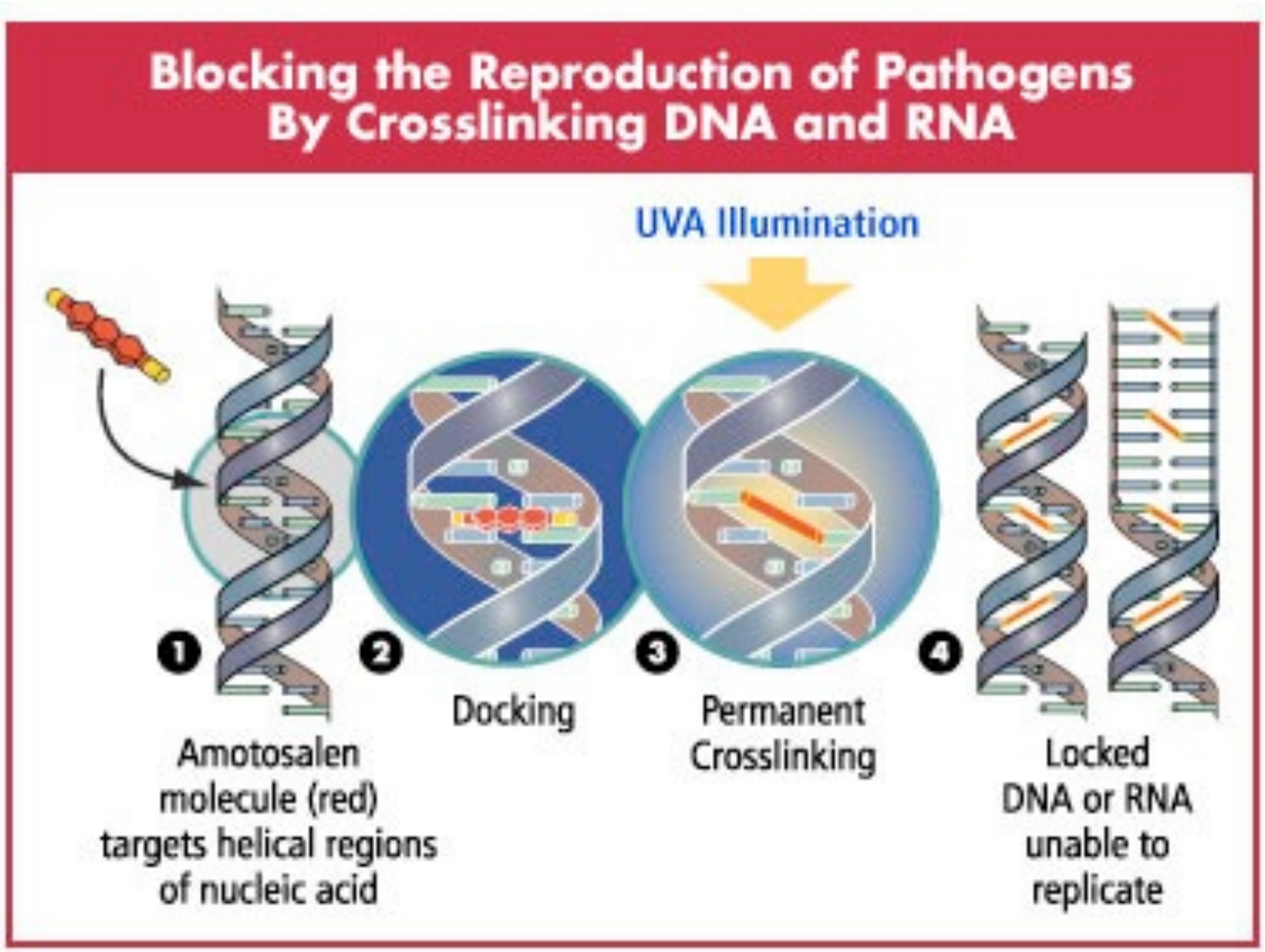
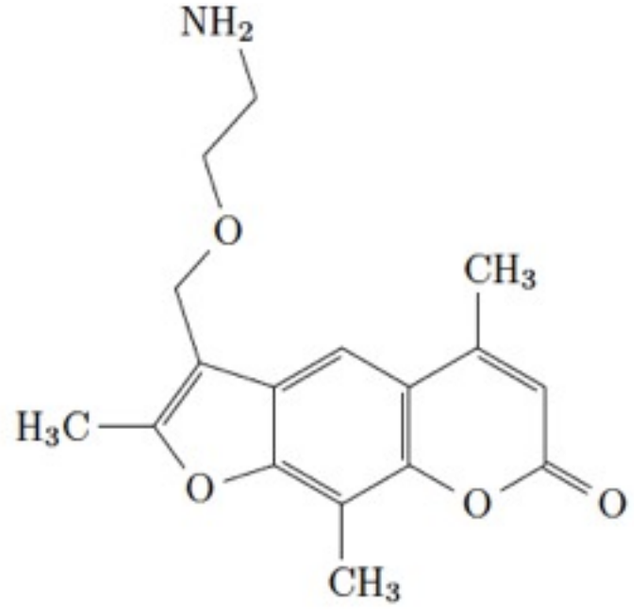
# Outline

- The Intercept technique for plasma - guardbands
- Sources of plasma
  - plasmapheresis
  - whole blood plasma
- Status of the project

# The Intercept process

Process very similar to platelets




Amotosalen

# The Intercept guardbands

| | Min | Max |
|---|---|---|
| Volume (including anticoagulant) | 385 mL | 650 mL |
| Red blood cells | | $4.10^9$ /L |

# The Intercept process

- Final product: 200 ± 20 mL
- In-process loss: 30 mL
- 385 mL < Vol < 430 mL: 1 final bag
- 430 mL < Vol < 630 mL: 2 final bags
- 630 mL < Vol < 650 mL: 3 final bags

Complete freezing within 20 hours post-donation.

# Authorized sources of plasma

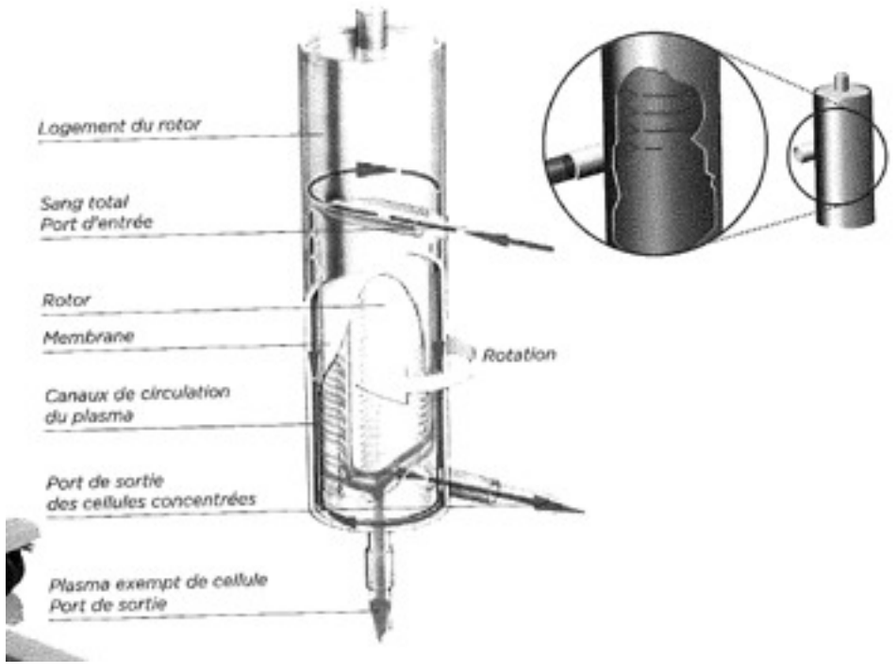
- Single-donor plasmapheresis
- Single donor concurrent plasma (collected during multicomponent apheresis)
- Pooled whole blood plasma (2-6 donors)
- Thawed plasma from any of the three sources (to be refrozen or transfused rapidly)

# Plasmapheresis specifications

- We want to collect:
    - 385 mL < Vol < 430 mL: one final bag
    - 430 mL (min 390 mL) < Vol < 630 mL: two final bags
    - 630 mL (min 570 mL) < Vol < 650 mL: three final bags
- No cellular contamination (<$4.10^9$ RBC/L; < 1, 2 or $3.10^6$ WBC/bag; PLT < $50.10^9$/L).
- WIthout saline compensation, the volume collected from the donor must not exceed 600 mL.

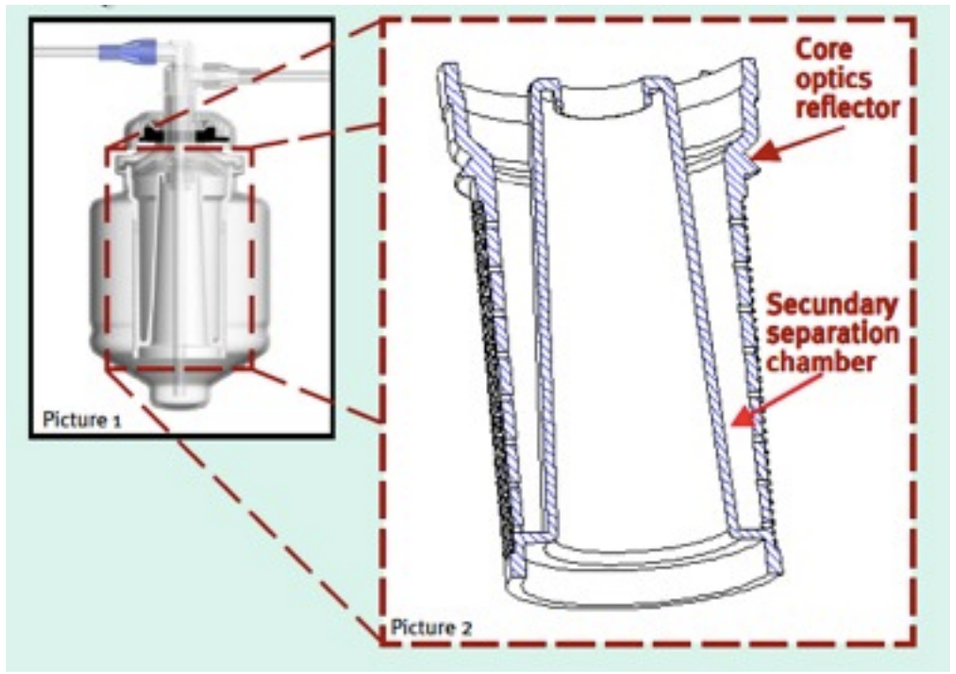
# Autopheresis-C, Fenwal

- Continuous centrifugation / filtration
- Yields essentially acellular plasma
- Plasma is continuously weighted
- collection duration: 45-50 minutes

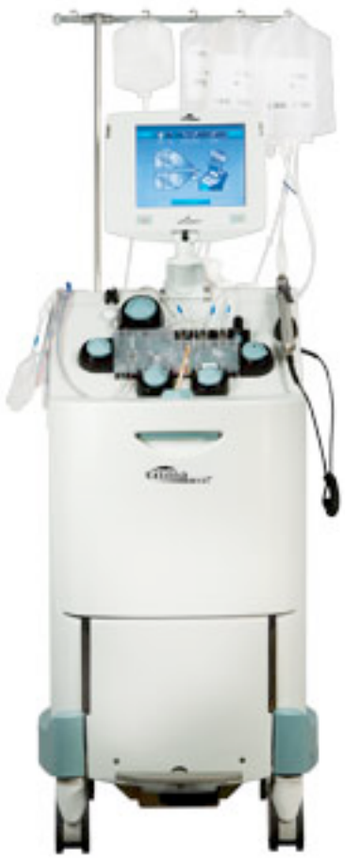


# PCS2, Haemonetics

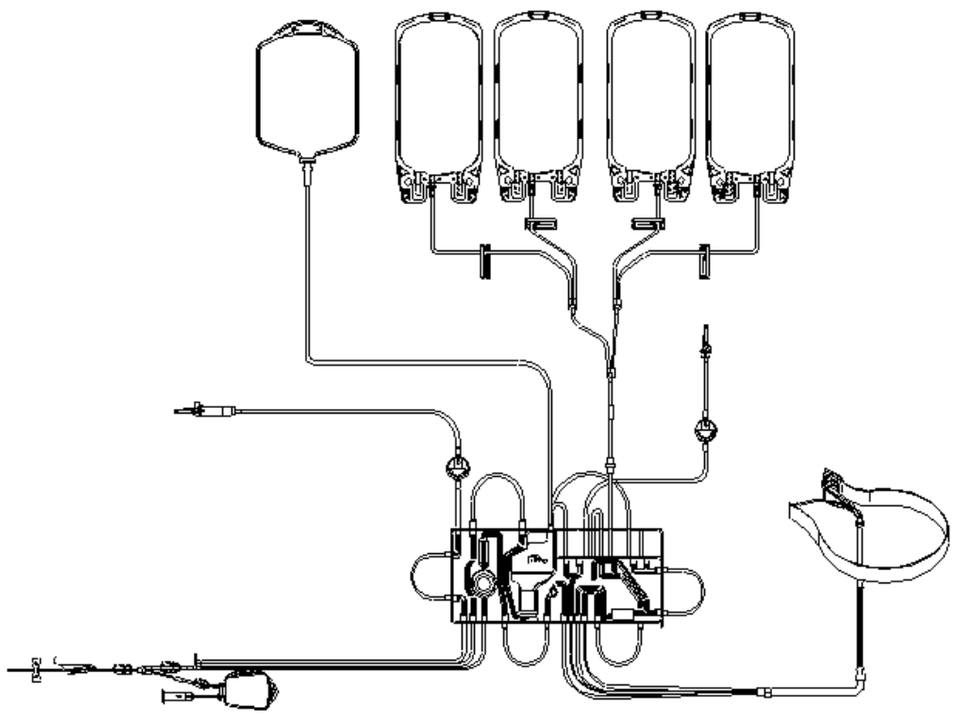

- Filling / centrifugation / extraction from a bowl (275 mL).
- Yields essentially acellular plasma (HSC Bowl)
- Plasma is continuousl weighted
- collection duration: 45-50 minutes



# Trima, Terumo BCT



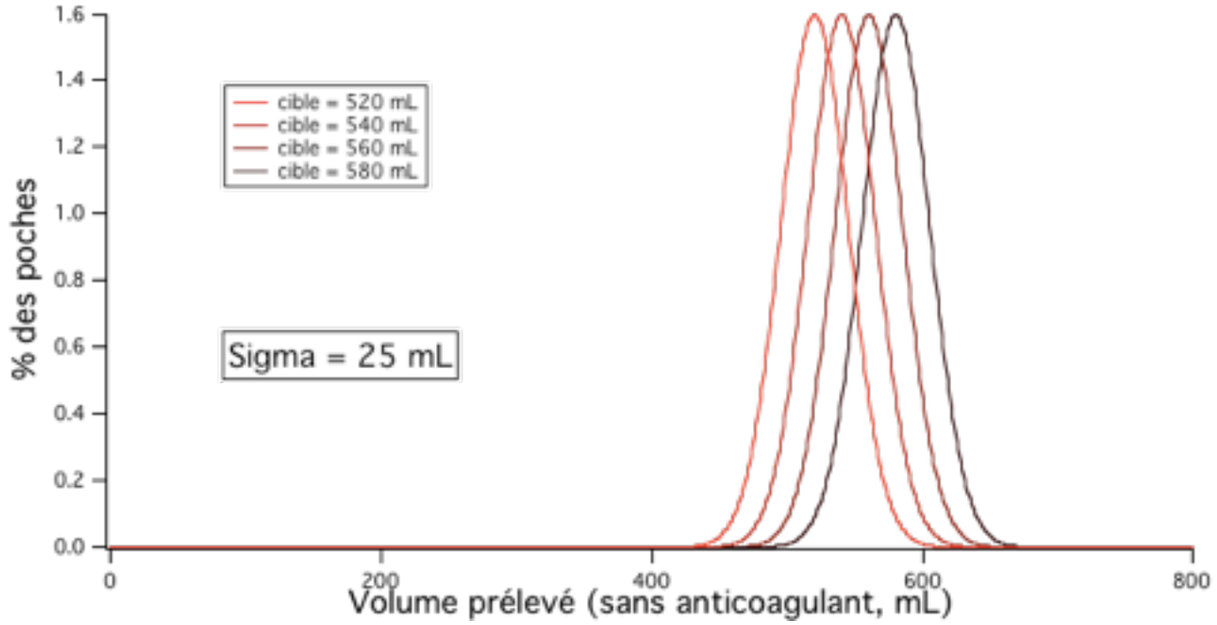
- Continuous centrifugation in a ring
- Yields essentially acellular plasma
- Final plasma volume is controlled by the pump cycle numbers
- collection duration: 30 min



# Collected volumes

- In Lausanne, we have decided to limit the collected volume at 600 mL (without anticoagulant) to avoid saline compensation
- In order to maximize the number of “triple-doses” (630-650 mL including anticoagulant), the collection has to be very reproducible

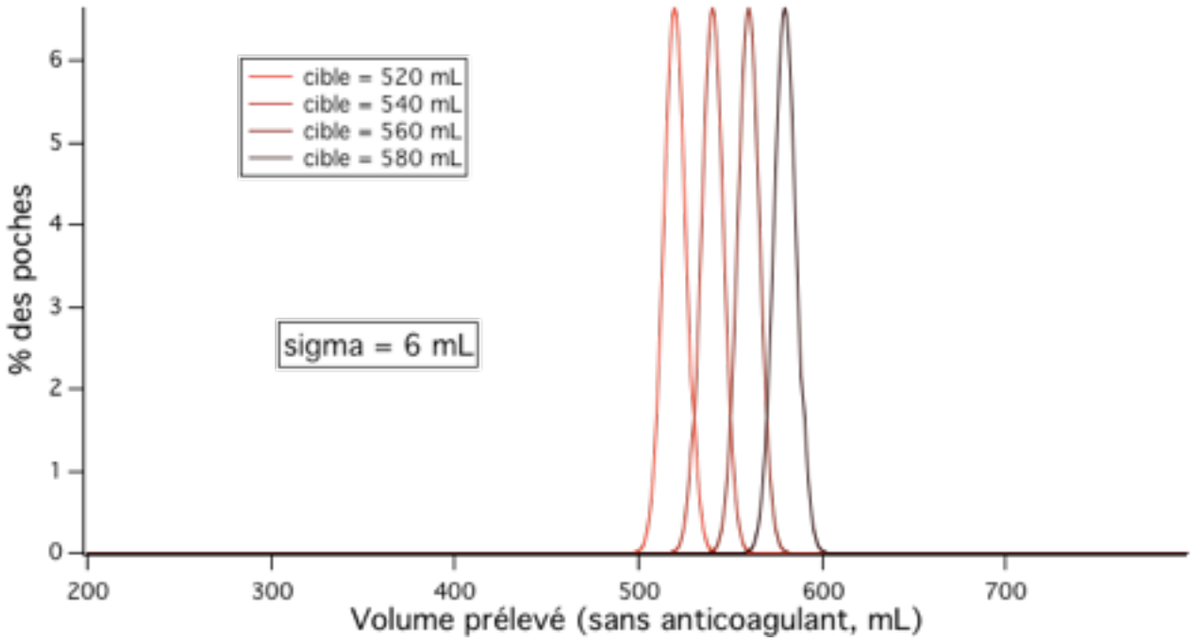
# Calculations of high variability collection




Collection NC

| | µ-3s | µ+3s | > 600 mL |
|---|---|---|---|
| Target = 520 mL<br>sigma=25 mL | 445 mL | 595 mL | 0.06% |
| Target =540 mL<br>sigma=25 mL | 465 mL | 615 mL | 0.8% |
| Target =560 mL<br>sigma=25 mL | 485 mL | 635 mL | 5.5% |
| Target = 580 mL<br>sigma = 25 mL | 505 mL | 655 mL | 21.2% |

# Calculations of low variability collection (sigma=6 mL)




Collection NC

| | µ-3s | µ+3s | > 600 mL |
|---|---|---|---|
| Target = 520 mL<br>sigma=6 mL | 502 mL | 538 mL | 0 |
| Target =540 mL<br>sigma=6 mL | 522 mL | 558 mL | 0 |
| Target =560 mL<br>sigma=6 mL | 542 mL | 578 mL | 0 |
| Target = 580 mL<br>sigma = 6 mL | 562 mL | 598 mL | 0.04% |

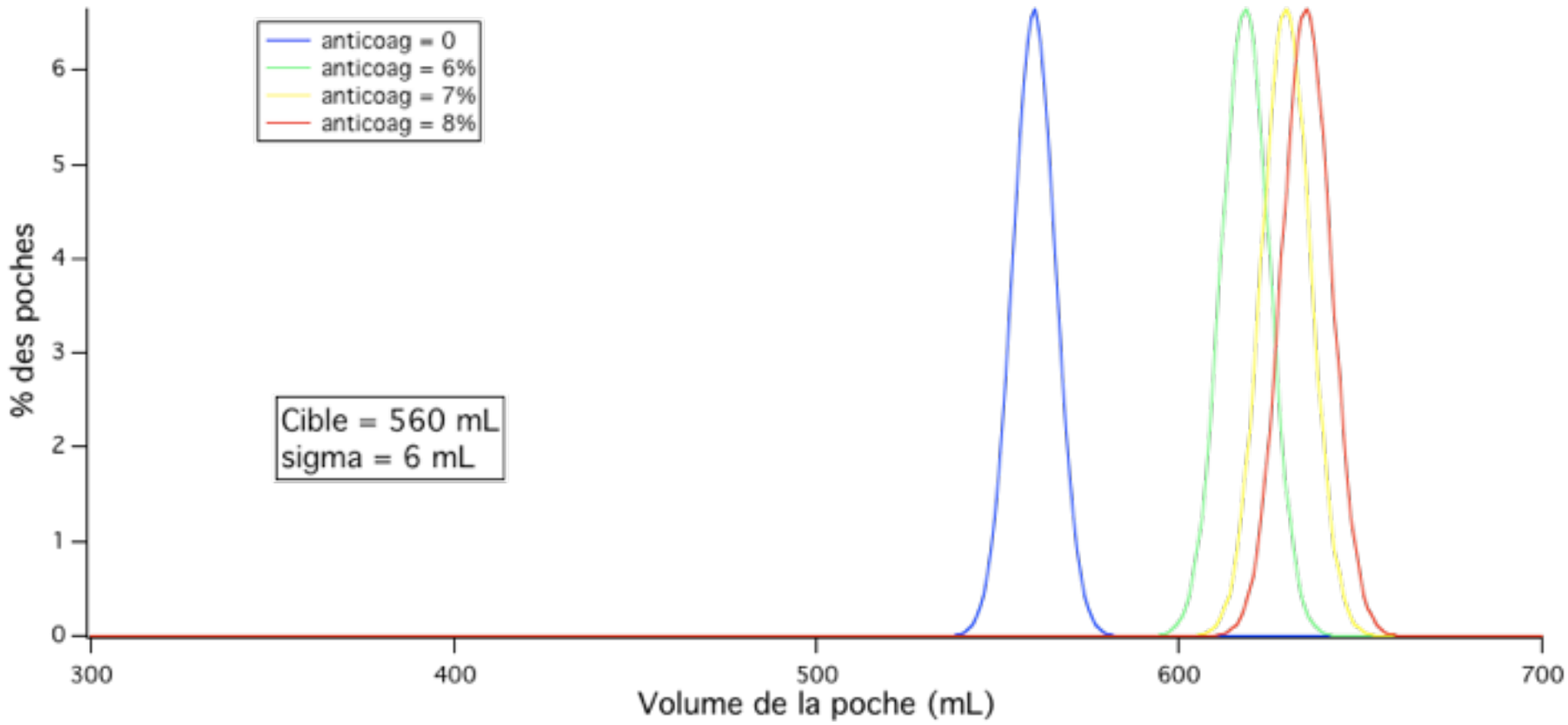
# Anticoagulation

- In-process loss during Intercept treatment is ca 30 mL.

- Once the target volume has been set without anticoagulant, the only possible adjustment is the anticoagulation ratio.

# Anticoagulation

- Classical anticoagulation: sodium citrate 6-8% (final concentration)



# Calculation of triple-doses (high variability)

| Target = 520 mL<br>sigma = 25 mL | < 385 mL | 385-430 mL | 430-630 ml | 630-650 ml | > 650 mL |
|---|---|---|---|---|---|
| AC=0 | 0 | 0 | 100% | 0 | 0 |
| AC=6% | 0 | 0 | 97.9% | 1.8% | 0.3% |
| AC=7% | 0 | 0 | 94.7% | 4.3% | 1.0% |
| AC=8% | 0 | 0 | 92.2% | 6.0% | 1.8% |

| | Sodium citrate concentrations (%) | | |
|---|---|---|---|
| Measure | 6 | 7 | 8 |
| Citrate (mmol/L) | 14.2<br>(13.3-15.4) | 16.9†<br>(15.1-18.3) | 18.3†<br>(14.6-20.6) |
| Sodium citrate (% of total plasma volume) | 10.4<br>(9.6-12.4) | 12.4†<br>(11.0-13.9) | 13.4†<br>(10.8-15.7) |

# Calculation of triple-doses (low variability)

| Target = 560 mL<br>sigma = 6 mL | < 385 mL | 385-430 mL | 430-630 ml | 630-650 ml | > 650 mL |
|---|---|---|---|---|---|
| AC=0 | 0 | 0 | 100% | 0 | 0 |
| AC=6% | 0 | 0 | 96.2% | 3.8% | 0 |
| AC=7% | 0 | 0 | 53.3% | 46.6% | 0.1% |
| AC=8% | 0 | 0 | 23.0% | 75.6% | 1.4% |

| | Sodium citrate concentrations (%) | | |
|---|---|---|---|
| Measure | 6 | 7 | 8 |
| Citrate (mmol/L) | 14.2<br>(13.3-15.4) | 16.9†<br>(15.1-18.3) | 18.3†<br>(14.6-20.6) |
| Sodium citrate (% of total plasma volume) | 10.4<br>(9.6-12.4) | 12.4†<br>(11.0-13.9) | 13.4†<br>(10.8-15.7) |

# Calculation of triple-doses (low variability)

| Target = 570 mL<br>sigma = 6 mL | < 385 mL | 385-430 mL | 430-630 ml | 630-650 ml | > 650 mL |
|---|---|---|---|---|---|
| AC=0 | 0 | 0 | 100% | 0 | 0 |
| AC=6% | 0 | 0 | 54.3% | 45.6% | 0.1% |
| AC=7% | 0 | 0 | 5.7% | 85.9% | 8.4% |
| AC=8% | 0 | 0 | 0.8% | 69.4% | 29.8% |

| | Sodium citrate concentrations (%) | | |
|---|---|---|---|
| Measure | 6 | 7 | 8 |
| Citrate (mmol/L) | 14.2<br>(13.3-15.4) | 16.9†<br>(15.1-18.3) | 18.3†<br>(14.6-20.6) |
| Sodium citrate (% of total plasma volume) | 10.4<br>(9.6-12.4) | 12.4†<br>(11.0-13.9) | 13.4†<br>(10.8-15.7) |

# Influence of anticoagulation on plasma quality

| | Sodium citrate 6% | Sodium citrate 8% | Difference (%) | p-value |
|---|---|---|---|---|
| FVIII (UI/dL, one stage clotting assay) | 117 | 111 | 5.1 | 0.0001 |
| FVIII (UI/dL two-stage chromogenic assay) | 88 | 84 | 4.5 | 0.02 |
| Von Willebrand factor (UI/dL) | 103 | 101 | 1.0 | 0.78 |
| Fibrinogen (mg/dL) | 276 | 282 | 2.1 | 0.51 |
| FV (UI/dL) | 102 | 96 | 5.9 | 0.0001 |
| FVII (UI/dL) | 110 | 109 | 0.9 | 0.78 |
| FIX (UI/dL) | 136 | 115 | 15.8 | 0.009 |
| AT (U/dL) | 108 | 110 | 1.8 | 0.63 |

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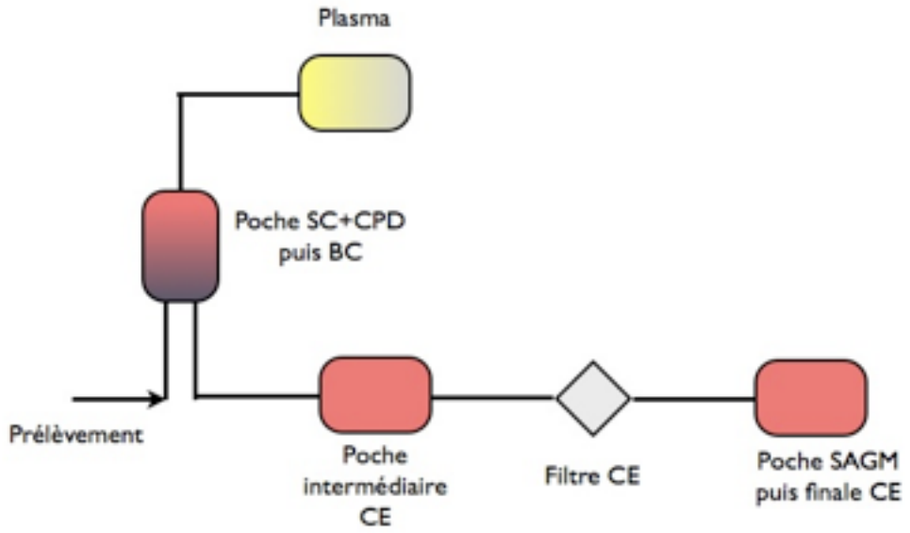
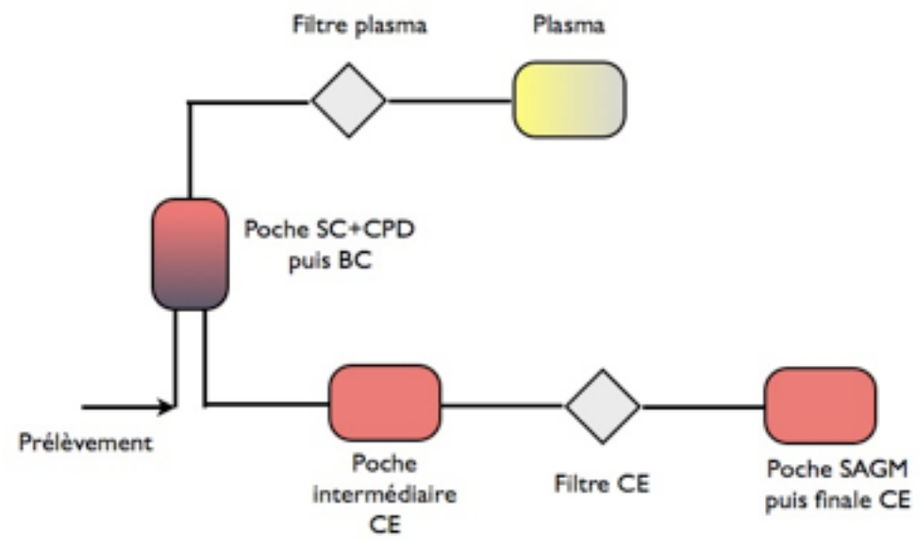
# Whole-blood plasma

# Intercept guardbands

- One needs to pool several whole-blood plasmas (260 mL) in order to comply to Intercept guardbands (385-650 mL)
- Swissmedic and T-CH authorized the pooling of 2-6 ABO matched whole blood plasmas
- One final plasma unit is 200±20 mL (mean of the production at 200 mL)
- Plasma must be leukocyte-reduced before Intercept

# Leukocyte reduction: integrated filter

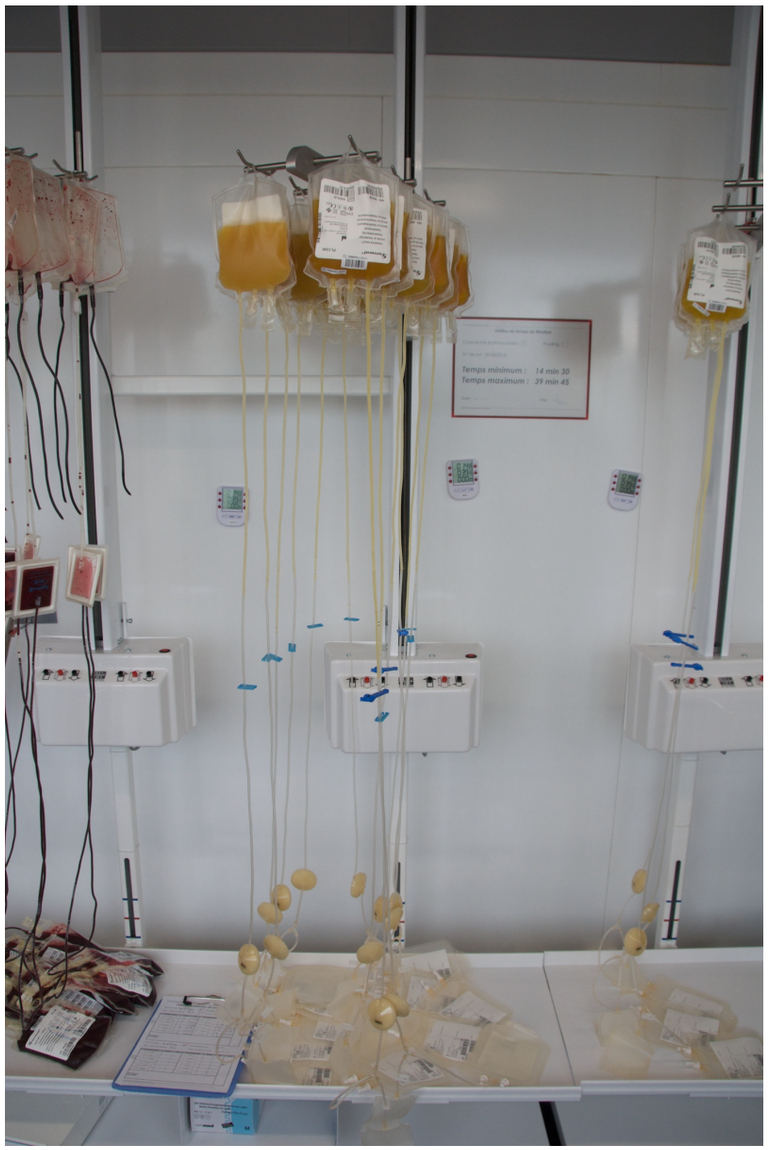



- Logistical constraints in collection units (two kits)

- Additional cost of 12-15 CHF

# Post-process filtration of unitary plasmas




Pall filter

Filtration time: 15 min

Dead volume: 7 mL

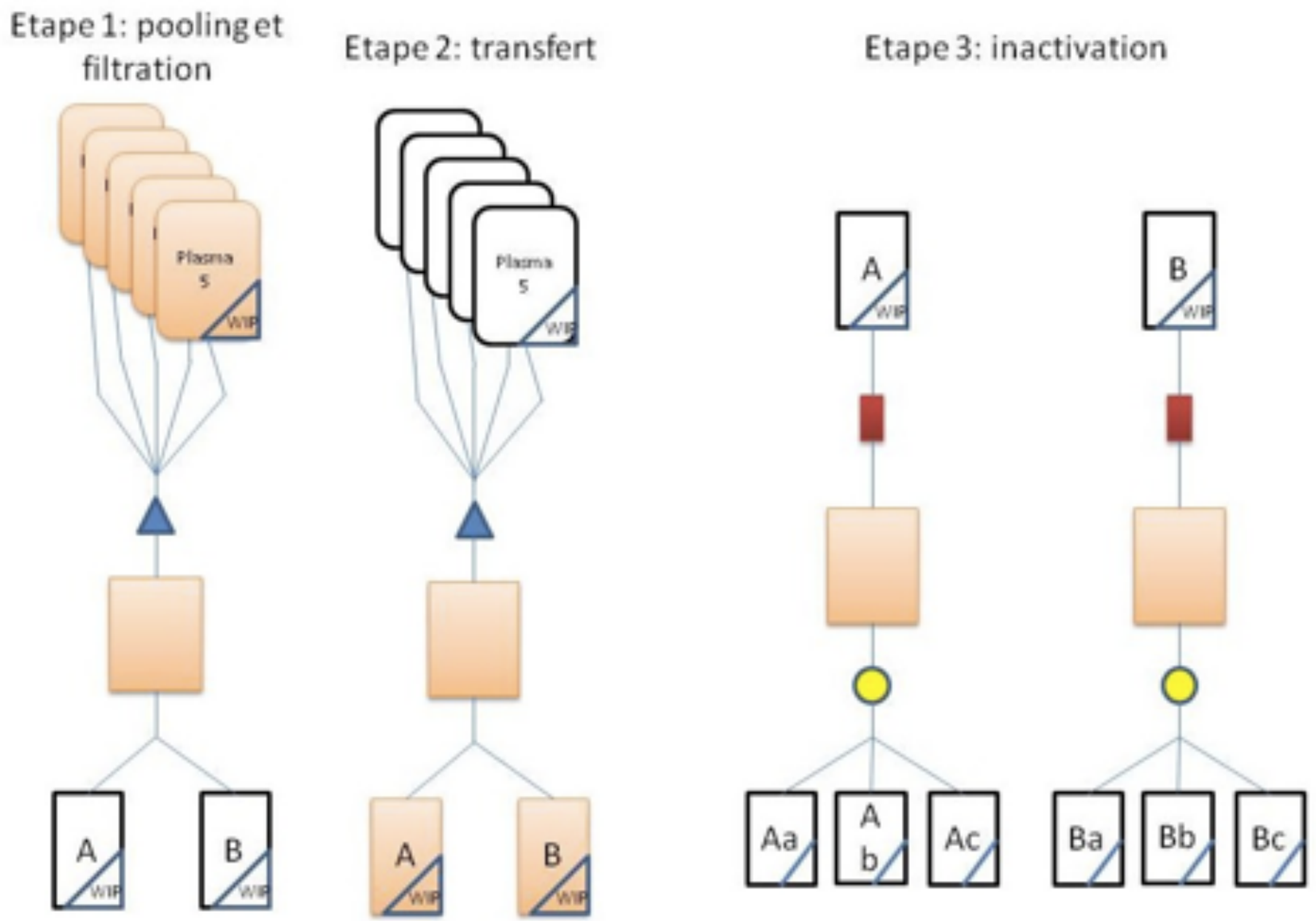
Cost: 13 CHF/plasma

# Filtration of unitary plasmas

- Each plasma is filtered individually (-7 mL/plasma), then 2-6 plasmas are pooled
- In-process losses of 30 mL

| Number of plasmas (260 mL) | Post-filtration pooled volume (mL) | Intercept kits \| losses (mL) | Final volume (mL) \| Number of plasmas \| Excedance (mL) |
|---|---|---|---|
| 2 | 506 | 1 \| 0 | 476 mL \| 2 \| 76 mL |
| 3 | 759 | 1 \| 109 mL | 620 mL \| 3 \| 20 mL |
| 4 | 1012 | 2 \| 0 mL | 952 mL \| 4 \| 152 mL |
| 5 | 1265 | 2 \| 0 mL | 1205 mL \| 6 \| 5 mL |
| 6 | 1518 | 2 \|  218 mL | 1240 mL \| 6 \| 40 mL |

# Filtration / pooling in a single kit



# Filtration / pooling

- There is no commercial kit available
- Developments are ongoing.
- Advantages:
  - limitation of sterile connections
  - Limitation of bag labeling
  - minimization of in-process losses (e.g. 17 mL for a pool of 1300 mL)
  - minimization of costs

# Pool filtration

- Pools of 2-6 plasmas are filtered (losses of 17 mL per pool)
- In-process losses of 30 mL during Intercept

| Number of plasmas (260 mL) | Post-filtration pooled volume (mL) | Intercept kits \| losses (mL) | Final volume (mL) \| Number of plasmas \| Excedance (mL) |
|---|---|---|---|
| 2 | 503 | 1 \| 0 mL | 473 mL \| 2 \| 73 mL |
| 3 | 763 | 1 \| 113 mL | 620 mL \| 3 \| 20 mL |
| 4 | 1023 | 2 \| 0 mL | 962 mL \| 4 \| 162 mL |
| 5 | 1283 | 2 \| 0 mL | 1223 mL \| 6 \| 23 mL |
| 6 | 1543 | 2 \| 243 mL | 1240 mL \| 6 \| 40 mL |

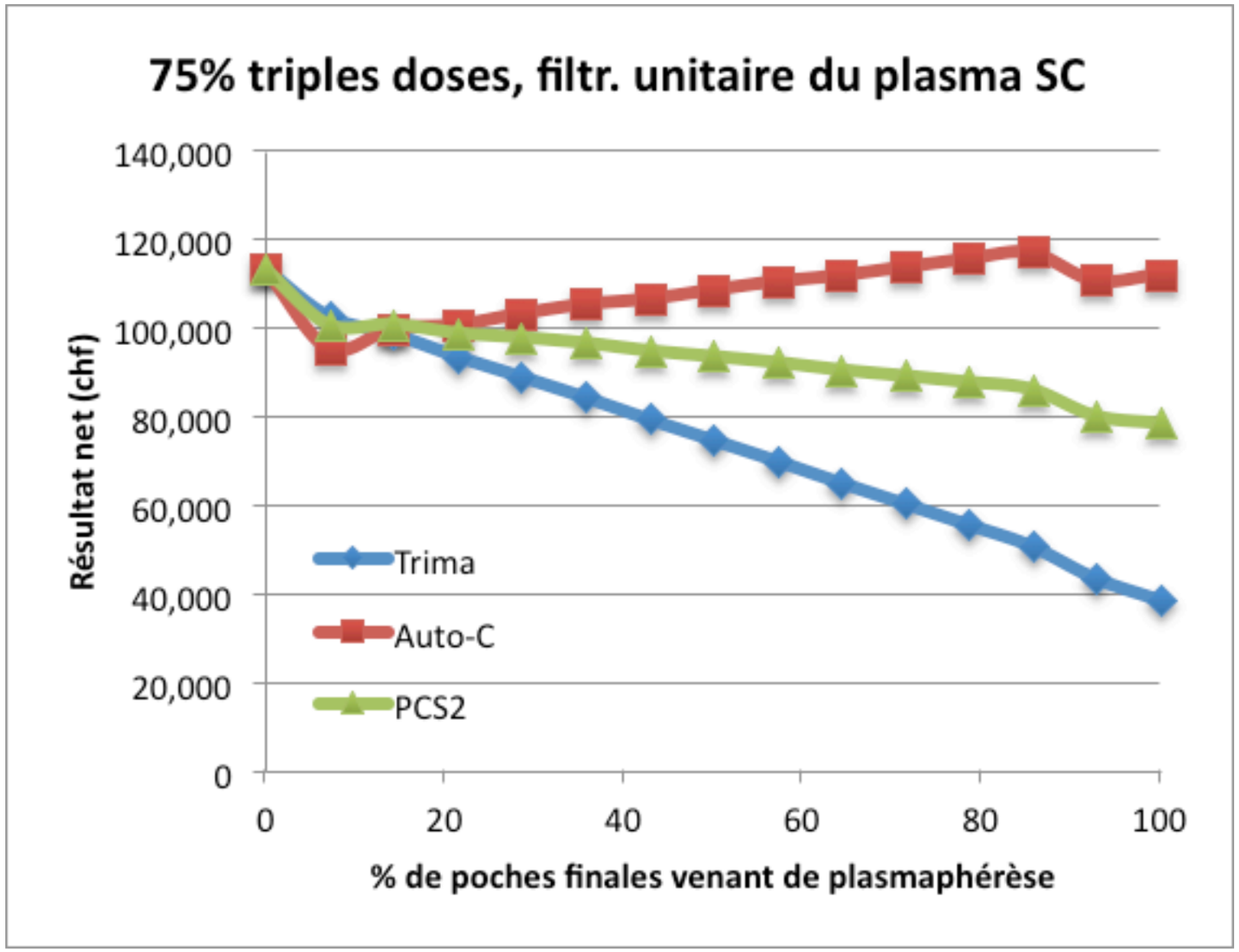
# Cost analysis in Lausanne

Hypotheses:

- Pooling of 5 plasmas to produce 6 final bags
- The loss of fractionation plasma is taken into account
- SCD=2.80 CHF; Intercept= 122.20 CHF

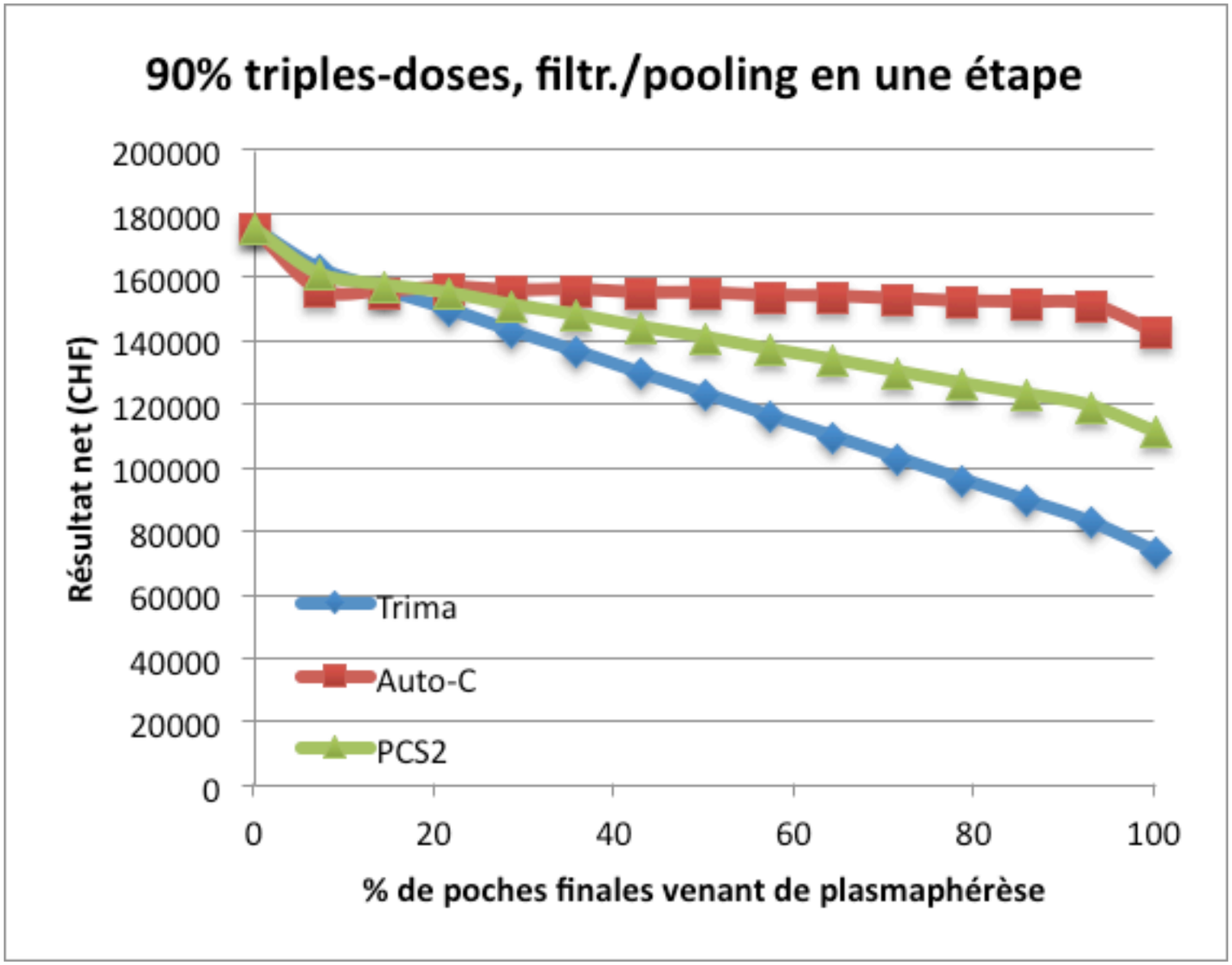
- Final bag cost (only material):
  - whole-blood: 78-87 CHF
  - plasmapheresis: 85-100 CHF
  - concurrent plasma: 84 CHF

# Worst case scenario




For 7000 bags of 200 mL

# Best-case scenario



# Project status

# Regulatory aspects

- Process approved by Swissmedic in late 2010 (treatment and freezing within 8 hours, Factor VIII > 0.7 UI/mL in final units)

- Modification of the approval in May 2011: treatment and freezing within 20 hours, Factor VIII > 0.5 UI/mL

- Modification to be filed by Cerus: suppression of the guardband on leukocytes, possibility to pool apheresis plasma

# Validation plan

- Very similar to platelets: one national validation plan with two (?) pilot centers

- Pre-validation: preparation of 12 units of plasma ready for Intercept to demonstrate the compliance to guardbands (volume, RBC) and establish baseline values for Fibrinogen and Factor VIII.

- Validation: 12 Intercept processes with same type of plasma, to check that the process is under control (retention of Fibrinogen and Factor VIII, amotosalen residual levels) and compliance to Swiss regulations for final units (Factor VIII absolute values, leukocyte contaminations)

# Planning

- The revision of the national validation plan will be submitted to Swissmedic next week.

- If everything is OK for Swissmedic, validation could take place in Lausanne and Zurich in October-November.

- Routine in .....?

# Thanks for your attention