Feasibility study freeze-dried plasma

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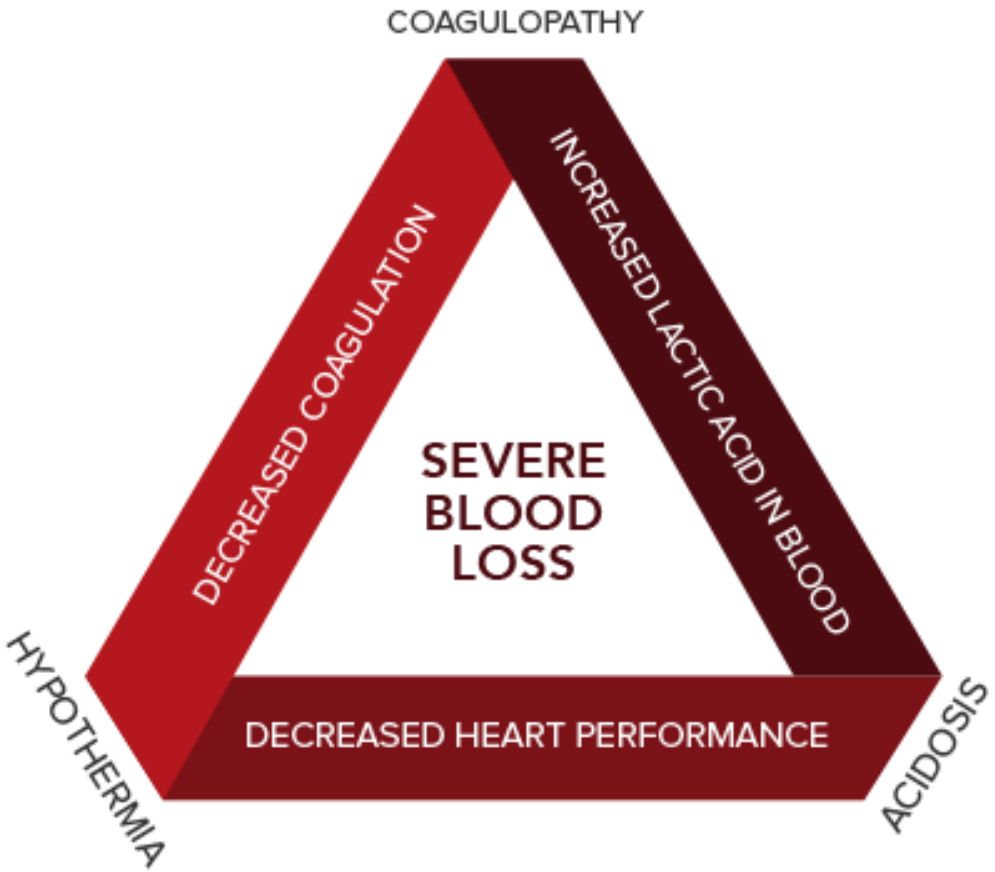
Coagulopathy of trauma



U.S. Military Involvements & Massive Transfusion Management

- World War I: vascular collapse was thought to be caused by toxins
- World War II: plasma was the resuscitation fluid of choice; ATN was recognized as a consequence of hypovolemic shock
- Korea & Vietnam: concerns of ARDS in setting of fluid resuscitation
- Iraq & Afghanistan: MTP development and use of fresh whole blood

Coagulopathy of trauma

- Higher ratio RBC : FFP = increased survival
- PAMPer-trial
  - 30-day mortality 30% vs. 23%, NNT 10
- COMBAT-trial
  - No difference
- Fresh frozen plasma
  - Requires cold chain
  - Thawing time
  - Wasting if thawed “on the shelf” and not used

PROPPR
Pragmatic, Randomized Optimal Platelet and Plasma Ratios

JAMA. 2015;313(5):471-482. doi:10.1001/jama.2015.12

Prehospital Plasma during Air Medical Transport in Trauma Patients at Risk for Hemorrhagic Shock

N Engl J Med 2018;379:315-26.

Plasma-first resuscitation to treat haemorrhagic shock during emergency ground transportation in an urban area: a randomised trial

Lancet 2018; 392: 283–91

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TABLE 1. Historical dried plasma development

Event
1930s Plasma lyophilization developed in the 1930s.
1940—Large scale production of pooled, lyophilized plasma by both the US and British established for war time use (to meet logistical constraints of whole blood and frozen/liquid plasma).
1941—Spray dried plasma produced for the Swedish Defense Department.
WWII Production
British produced >500,000 U lyophilized plasma during WWII.
US produced >6,000,000 U lyophilized plasma during WWII.
US/British distributed world-wide.
Sweden produced approximately 17,000 U spray dried plasma for Sweden and Finland.
1945—Hepatitis
Hepatitis as a result of plasma transfusion recognized by the end of WWII.
Believed that benefits outweighed the risk.
1945-1952—Hepatitis
Attempts at pathogen reduction and reducing pool size not successful.
Several deaths in clinical studies of ultraviolet irradiated pooled plasma.
1953—Department of the Army (Circular 73) directed that, because of the risk of serum hepatitis, the higher cost, and the need to use it for the production of specific globulins, plasma would not be used "to support blood volume" unless dextran was not available.
1953—Serum albumin replaced plasma as primary resuscitative product for US Forces in Korea.
1968—National Research Council Committee on Plasma and Plasma Substitutes recommended that "the use of whole, pooled human plasma be discouraged and even discontinued unless a clear cut case can be made for its unique requirements."
The French Military Blood Institute produced dried plasma from 1949 to 1984, and provided over 40,000 units to French military forces during the Indochina War. In 1985, production was discontinued due to risk of HIV infection.

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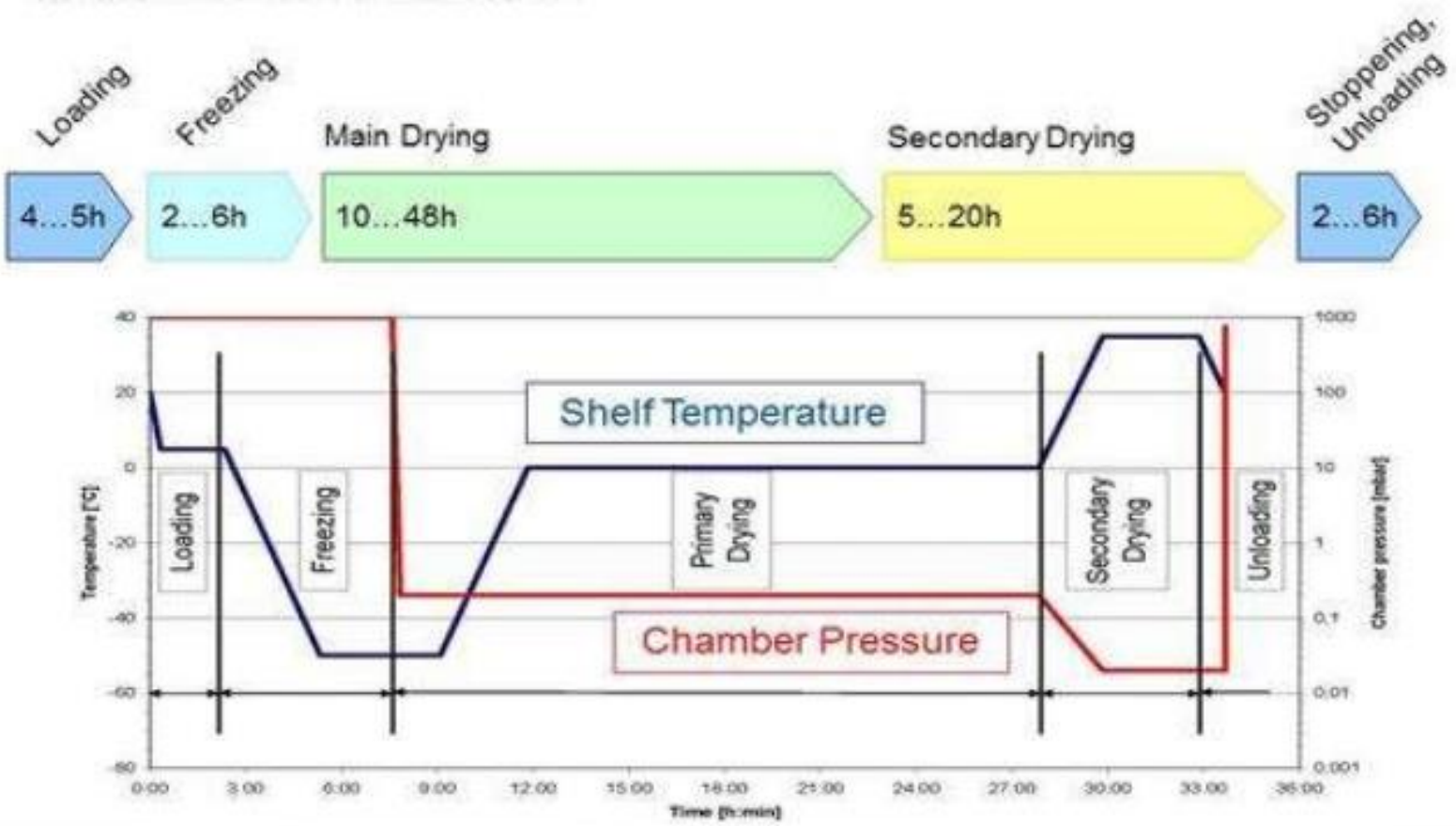
Typical Freeze Drying Cycle



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Dutch hospitals

- Doctors familiar with freeze-dried plasma due to work abroad (anethesiologists trained in Germany)

- Wish to have freeze-dried plasma available
  - Pre-hospital on trauma-helicopter
  - Massive transfusion protocol

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TABLE 2. Characteristics of commercially available dried plasmas

	FLYP	LyoPlas N-w	Bioplasma FDP
Use	1994-present—French Military 2011-present—Civilian (austere)	General population—Germany	General population—South Africa & neighboring countries
Processes	• Lyophilized • Pooled apheresis FFP <11 donors • All volunteer donors • Donor screening • Testing—disease & factors • Hemovigiliance program • 2003—Leukoreduced • 2010—No HLA Ab+ women • 2010—Amotosalen PR	• Lyophilized • 1990-2006: Pooled S/D • 2007-present—Single Donor • Donor screening • Hemovigilance Program • Frozen >/= 4 mos for donor retest • Leukoreduced • No HLA Ab+ women	• Lyophilized • Pooled (up to 1,500 donors) • All volunteer donors • Donor screening • Comprehensive testing • Hemovigilance program • S/D treatment for PR
Characteristics	• Normal factor levels • ABO-universal	• Normal factor levels • ABO type specific	• Factor levels: >/= 0.40 IU • ABO-universal plasma
Shelf-life	2 years at room temperature	15 months at 2°C-25°C	Store below 25°C
Reconstitution	<6 minutes	A few minutes	<10 minutes
Indication	As sole source of plasma where used	Same as frozen plasma	Where plasma and/or coagulation factors are required
Safety	No adverse events reported (including TRALI) since 1994 start of hemovigiliance program	• >300,000 U S/D LyoPlas • >230,000 U LyoPlas N-w (2007-2013) • Hemovigilance program reported no increase incidence of adverse events	Contraindicated: Severe Protein S deficiency • Hemovigilance program—no increase in adverse events
Efficacy	Clinical use reports support efficacy as part of a 1:1 DCR approach[12]	No restrictions related to clinical efficacy have been identified	No restrictions related to clinical efficacy have been identified

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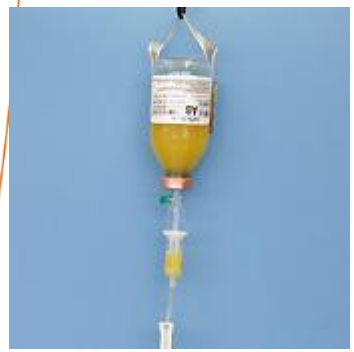
Set Lyoplas-NW



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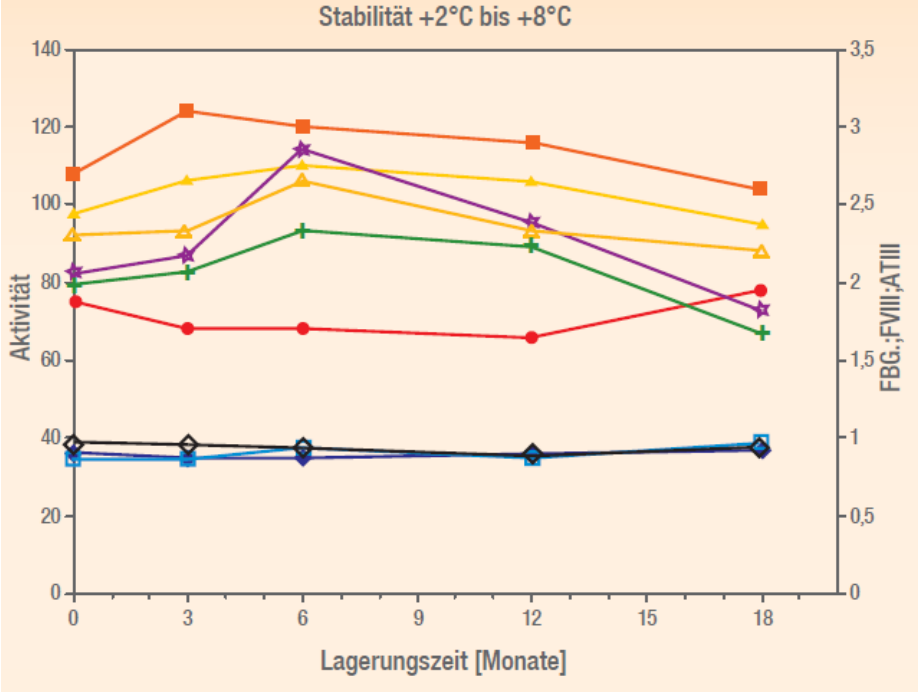
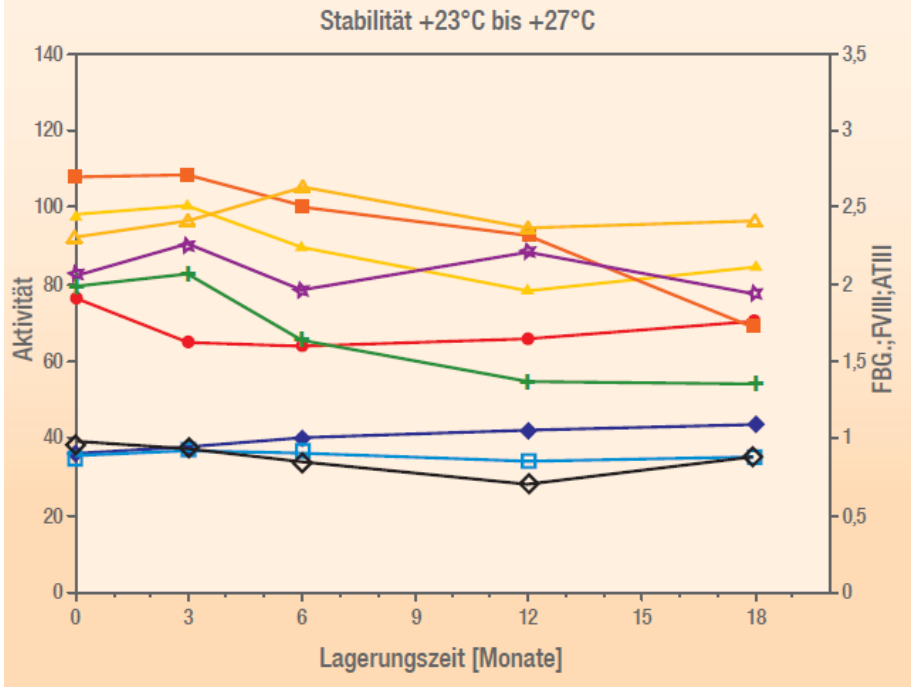
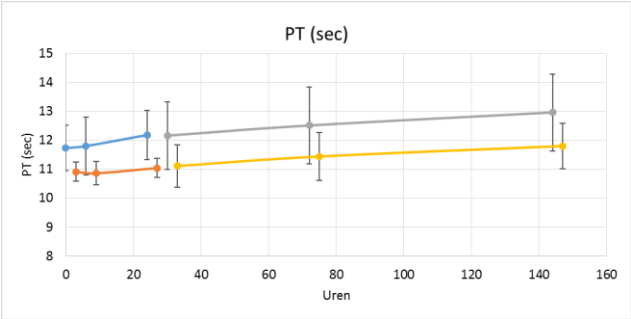
Stability

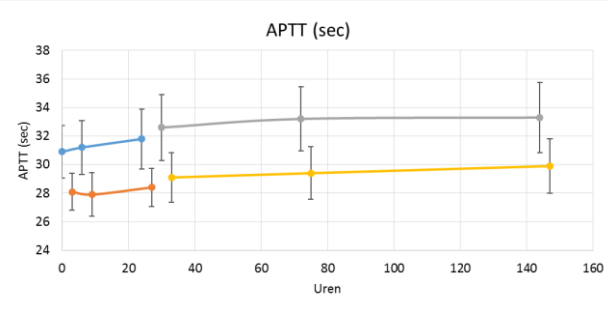


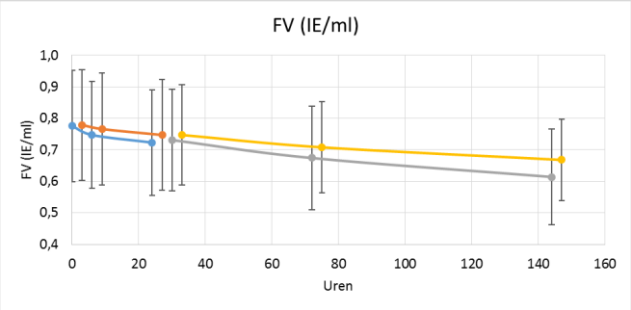


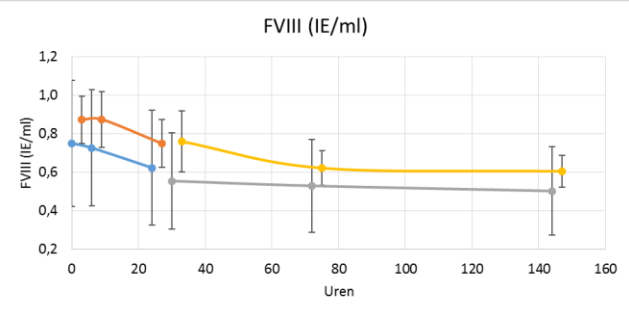
PTT [s] Faktor V [%] Faktor XI [%] Protein S [%]
vWf/RiCoF [%] Plasminogen [%] Fibrinogen [g/l] Faktor VIII [IE/ml] AT III [IE/ml]

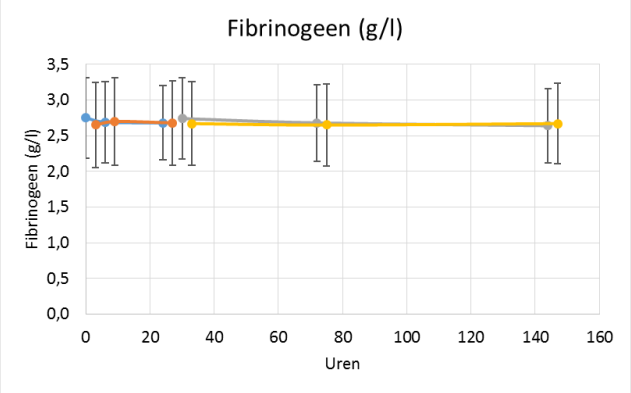
Bux et al. Hämotherapie 2009; 13: 33-37.

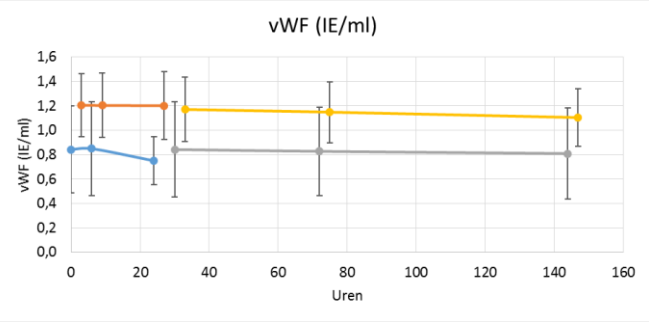












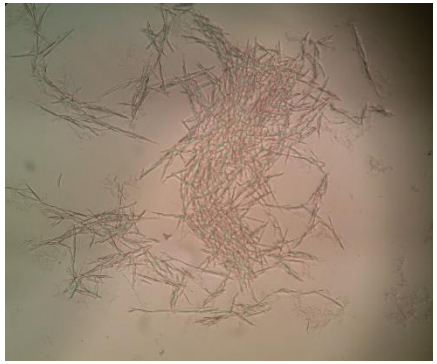
- Lyoplas KT n=10
- Plasma KT n=10
- Lyoplas 4°C n=10
- Plasma 4°C n=10

KT = room temperature

“Needles”

- 2013 the miilitary blood bank found that the”swirling” seen Lyoplas-NW (and the French freeze-dried plasma also) was due to microscopic ”needles”
- Size 1-9 µm
- German Red Cross
  - floating probable lipid
  - comparable with LyoPlas extracts, therefore no enrichment of cholesterol or other lipids
  - Adjustment of freeze-drying proces, reduction of 90% of ”needles”

”Needles” in LyoPlas



“Needles ” in 1% Triton washed LyoPlas

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And now?

- Dutch hospitals want to use freeze-dried plasma
  - Massive transfusion protocol
  - Trauma-Helicopter
- Feasibility studie planned
  - Handling
  - Logistics / Traceability in hospital / pre-hospital setting
  - Wasting
  - *Not:* effectiveness, mortality

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Study proposal

- Use of Lyoplas N-W
  - Single-donor plasma German Red Cross, non-renumerated donors
- 4-5 traumacentra with / withouthelicopter
  - Pre-hospital on helicopter (new in NL)
  - Massive transfusion protocol (CSO, OK, obstetrics)
- Measuring
  - Wastage of plasma compared to the same period the previous year
  - Time from ordering until administration (in-hospital (& pre-hospital) logistics)
  - Time needed for dissolving
  - Problems encountered at dissolving (foam, etc)
  - Ease of use / content of hospital/helicopter staff with handling the product
  - *Not:* patient related outcomes

Study proposal(vervolg)

- Duration
  - Estimated 80-100 vials per centre enough
    - To let different staff members form an impression of the product
    - Getting feedback of different staff-members
  - Trauma-centres asked:
    - Monthly thawing of 10-20 Omniplasma for massive transfusion protocol

  ➢ estimated 3-5 months duration

- Reporting
  - Consortium
  - LGR
  - RGR
  - BTC’s participating hospitals (and other BTC’s if interested)

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